Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

AUGUST—1959
Volume 9 . . . 8

MARCH 4, 8:10 A.M.
Acutely agitated,
destructive and assaultive,
uncommunicative.

RCH 4, 10:00 A.M.
ARINE, I.V., has been given.
tient in light sleep.
n be awakened readily,
d responds to questioning.

MARCH 5, 2:00 P.M.
Receiving oral SPARINE.
Quiet but alert. Contrite
about smashed window.

MARCH 8, 9:00 A.M.
Still on oral
SPARINE, maintenance
dosage. Ready
for psychotherapy.

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Volume 9 **Neurology** *Number 8*

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*Livingston, S., and Petersen, D.: New England J. Med. 254:327 (Feb. 16) 1956.

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1. Doshay, L. J. et al.: J.A.M.A. 160:348 (Feb.) 1956
2. Berris, H.: J.-Lancet 74:245 (July) 1954.

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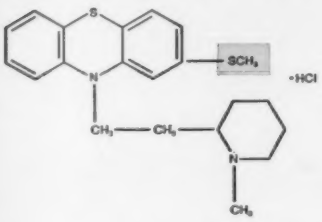

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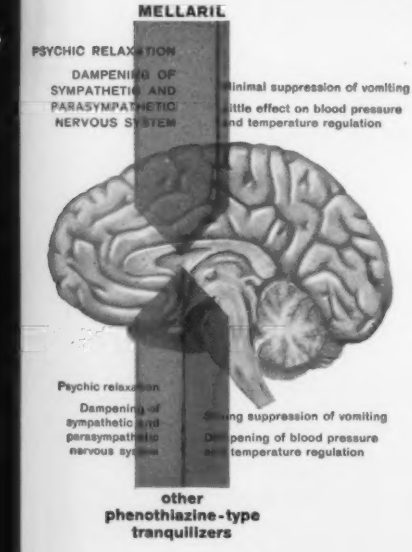
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Little effect on blood pressure
and temperature regulation
Psychic relaxation
Dampening of sympathetic and parasympathetic nervous system
Suppression of vomiting
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*Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959

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*Carter, S.: *M. Clin. North America:* 315 (March) 1953.

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*W.A. Leff, *Antibiotic Med. & Clin. Therapy*, 6: (Suppl. 1), 44-48, Feb. 1959.

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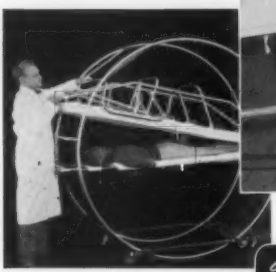

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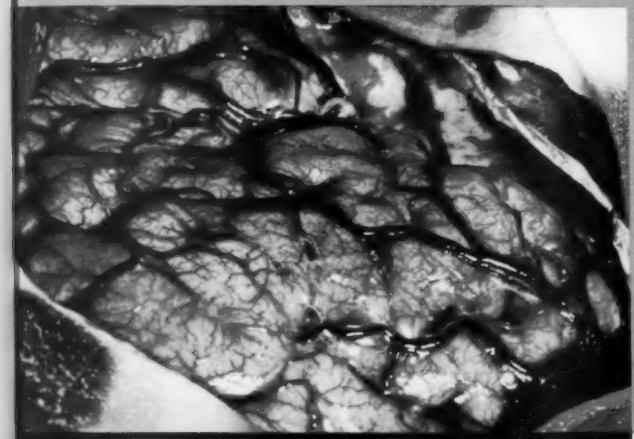

ABOVE: The effect of 1 Gm. of intravenous urea (3 cc. of Urevert) per kg. of body weight. The cortex lies well below the dura. Pressure is relieved. Visualization and space for manipulation are improved.

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[6]Javid, M.: Urea – New Use of an Old Agent, Reduction of Intracranial and Intraocular Pressure, S. Clin. North America *38*:907 (Aug.) 1958.

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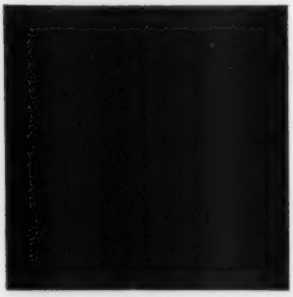
first report on a new and significant antidepressant



the new, rapidly effective treatment for true (endogenous) depressions, affective or organic

Nardil™

brand of phenelzine dihydrogen sulfate

restores the depressed, despondent or suicidal patient to reality without recourse to E.C.T.[1-4]

QUICK-READING SUMMARY

chemistry-pharmacology: Nardil, first discovered in 1956 by Scott and Chessin,[5] is beta-phenylethylhydrazine dihydrogen sulfate, a powerful inhibitor of monoamine oxidase in the brain.[6]

clinical response: many depressed patients respond with an elevation of affect within 4 to 8 hours. Self-deprecatory feelings and even suicidal ideation rapidly subside. Depression is lifted without the over-stimulation of sympathomimetic amines. Recovery generally occurs within 2-6 weeks. E.C.T. was not required.

side effects, toxicity: clinical trials since 1957 have revealed no toxic effects on blood, liver or kidneys. Few side effects have been encountered. However, dosage levels higher than recommended may produce transient postural hypotension, constipation, impotence or delayed micturition.

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first report on a new and significant antidepressant

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a brain-specific monoamine oxidase inhibitor

the new, rapidly effective treatment for true (endogenous) depressions, affective or organic

restorative activity apparent in hours

•

objective antidepressant response in days

•

complete recovery in 2 to 6 weeks

•

side effects transient and mild

Common among the experience reported by several investigators during the Nardil trials was this new drug's speed of action, high percentage of complete to good remissions, the absolute lack of toxicity and the infrequency and mildness of side effects.

Many patients report a lift in mood within four to eight hours. A new sense of purpose is accompanied by a rapid dispersal of self-deprecatory feelings, ruminative thinking and suicidal ideation. Sleep and appetite are improved.[1]

Sainz[2] reported that, of his series of 122 patients, 89 per cent of the depressed affectives and 82 per cent of other endogenous depressions had complete remissions following Nardil.

Maximum improvement was always noticed not later than five weeks after the onset of therapy.[2] This investigator then concluded that Nardil "...appears to be the treatment which most clearly compares to electrocoma therapy in scope, rapidity of action and freedom from serious side effects."[2]

This observation has also been made by Thal[1] as a result of his experience with Nardil in 180 patients with true (endogenous) depressions. "In the treatment of depression, the response to this antidepressant therapy approaches the response generally obtained from electro-shock therapy. Eighty per cent of patients were discharged from the hospital as recovered within 60 to 90 days following commencement of treatment with Nardil." Electroconvulsive therapy was not used in any case.

Saunders and colleagues[3] found that all their patients with true (endogenous) depressions recovered within 10 to 15 days of therapy with Nardil.

In over 1,000 patients to date: *liver dysfunction did not occur, clinical hypotension was rare.*

Nardil has a preferential distribution to the brain—not the liver. The investigations of Sainz[2] in 122

COMPARATIVE EFFECTIVENESS*

General diagnosis	Patients	ECT % Satisfactory Response	Iproniazid % Satisfactory Response	Patients	Nardil % Satisfactory Response
endogenous depression, overt	11	72	45	26	78
endogenous depression, larval	3	—	100	12	86
affective psychosis, depressed phase	8	87	42	19	89

*Adapted from Sainz, A.

moderate to markedly depressed patients revealed that Nardil was "...less toxic than iproniazid because no hepatic, hemopoietic or central nervous system parenchymatous damage (had) occurred or been foreshadowed." The experience of Thal[1] in 180 patients, and that of Saunders[3] as well, disclosed no toxic effect after careful analysis of liver function tests and blood studies.

Postural hypotension has appeared among a few patients given Nardil in a dosage range higher than that recommended.[2] But since the incidence does not appear to be clinically significant, it does not detract from Nardil's particular value in ambulatory as well as hospitalized patients.

Indications: Nardil is indicated in the treatment of true (endogenous) depressions of an affectual or organic nature. Depression associated with catatonic schizophrenia may be relieved, although Nardil itself has no effect on schizophrenic mechanisms.

Side Effects: The occasional side effects which have been reported include postural hypotension with the expected associated signs, transient impotence, nausea, ankle edema, delayed micturition and constipation. These can be adequately managed by appropriate adjunctive therapy or will abate as dosage is reduced to the maintenance level.

Caution: Even though no toxic effects on the liver have been reported with the use of Nardil, as a matter of caution patients should be carefully followed with liver profile studies and the drug should be withheld or used with extreme care where the patient has a history of liver disease or where liver damage is present. Also, hypotensive patients should be under close medical supervision.

Dosage: Recommended starting dose is one 15 mg. tablet three times a day with meals. Improvement is usually seen within one week. After maximum benefit is achieved, usually over a period of several weeks, the dosage is slowly reduced to a maintenance level depending upon individual needs and may be as low as 15 mg. daily. In the occasional patient who does not respond to the above starting dose, an additional one or two 15 mg. tablets may be given at bedtime.

Supply: Bottles of 100 orange-coated tablets, each containing 15 mg. phenylethylhydrazine present as the dihydrogen sulfate.

References: 1. Thal, N.: Cumulative Index of Antidepressant Medications. Dis. Nerv. System *20*:197 (May) 1959. 2. Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, Ann. New York Acad. Sc. (in press) 1959. 3. Saunders, J. C.; Roukema, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, Am. J. Psychiat. (in press) 1959. 4. Report of Clinical Trials with Nardil in 800 Patients. Warner-Chilcott Department of Clinical Investigation, 1959. 5. Chessin, M.; Dubnick, B.; Dramer, E. R., and Scott, C. C.: Modifications of Pharmacology of Reserpine and Serotonin by Iproniazid, Fed. Proc. *15*:409, 1956. 6. Chessin, M.; Dubnick, B.; Leeson, G., and Scott, C. C.: Biochemical and Pharmacological Studies of β-phenylethylhydrazine and Selected Related Compounds, Ann. New York Acad. Sc. (in press) 1959.

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Lerner, P. F.: Kemadrin, a New Drug for Treatment of Parkinsonian Disease, J. Nerv. & Ment. Dis. 123:79 (Jan.) 1956.

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Neurology Volume 9 • Number 8

Presidential Address

Francis M. Forster, M.D.

TRADITIONALLY, the address of the President may fall into one of three categories. He may present a scientific paper of his own choice, he may present a history of the Society, or he may give a general policy address and touch upon the relations of the Society to the field. For my own address, I have chosen a combination of history, development, and predictions for the future joined in a Toynbee approach.

History as a recitation of dates, places, and names becomes dull indeed. But history in the Toynbee tradition of "where have we been and where are we going" serves an extremely useful purpose. In fact, Santayana, the philosopher, said: "Those who do not recall the past are destined to relive it." This can be paraphrased to say that "those who recall the past may live a better future."

Let us recall then for a few moments the past history of the Academy. The Academy is so young that one might think that there is very little to say about its history. Neurologists with their interest in perinatal conditions should be most aware that the medical problems of life start long before birth. If we look at the Academy of Neurology in its gestation period, we find in the 1940's, particularly directly after the second World War, a very active group of then-young neurologists trying to fertilize the formation of the Academy and the renaissance of American neurology. Wherever there was a medical meeting with any relationship to neurology, a small group of ardent pro-neurology physicians would gather, discussing problems that beset neurology and planning what could be done about them. The nucleus of these groups was almost invariably Dr. A. B. Baker, and so when the Academy was formally organized he very naturally became its founding president.

The original nucleus of the Academy was largely Midwestern. The original organization called for a biannual meeting and oriented only toward clinical neurology. Despite, or perhaps because of, these limited parameters, the Academy quickly became a vibrant organization with a true identification for men devoted to clinical neurology. Even before the first meeting, the Academy was a truly national society and free of sectionalism. In one year, the biannual concept was dropped. The meetings were so successful and there was such a clamor for a meeting the next year that no interim between meetings occurred.

Being spearheaded by educators in neurology and by men who were zealous to improve their scientific status, the special courses of the Academy within a few years became a very vital part of the Academy. These were designed originally for the Junior Members and it was with surprise that the Board of Trustees and officers found that all of them were as in-

From the Department of Neurology, University of Wisconsin Medical School, Madison.

Read at the eleventh annual meeting of the American Academy of Neurology, Los Angeles, April 17, 1959.

terested in the courses as were the Junior Members. This, I believe, has done much for the true democracy of the Academy. Scientific exhibits were added and have been developed to a high degree by the effort first of Dr. Benjamin Boshes and later by his brother, Dr. Louis Boshes.

But the spoken word is not enough. The material given at the Academy was soon realized to be superb in its scientific evaluation, and the media for publication too few. The Academy, in its virile manner, set up a journal. In this endeavor, the Academy has always been indebted to Mr. Louis Cohen, the publisher, who assumed the costs for the first several years in order to launch a truly good journal. The title of the journal, with its succinctness, exhibits much of the philosophy of the Academy itself. The Board of Trustees and officers debated at length what to call the Journal, and at one point it was suggested that it be called the *American Journal of Clinical Neurology*. It was quite obvious that it was American, anyone could see that it was a journal, and some day, perhaps, it would not be all clinical, and as one member of the Board of Trustees and officers at that time facetiously remarked, "We could just settle and call it *Of*." However, the crisp and concise name of *Neurology* tells much of the Academy. *Neurology* was published bimonthly, but after two years the pressure of material necessitated monthly publication. And supplements have become a habit in the last two years! Dr. Russell DeJong has given the editorial leadership and industriousness that made this possible.

While the Academy began as a clinical neurology organization originally, men in other clinical areas and in the basic sciences were always welcome as members and, of course, to participate in the meetings. There was early a feeling that we needed more basic science material in our program, and later, when the journal was formed, there was considerable feeling that it was necessary to include basic science papers to make the journal a truly representative and worthwhile venture. And so, bit by bit, this came to happen. Then at the St. Louis meeting, the Academy officially formed the sections, predominantly in the basic sciences. The formation of the sections has met with some criticism, and, interestingly, the criticism is on the basis that one cannot get to everything that the Academy is now having. One cannot help but appreciate criticism such as this, because it is the highest accolade for the quality of the neurologic programs presented by the Academy. On the other hand, the sections, as they are envisioned and as they have come to fruition, offer a broader spectrum and serve a very worthwhile purpose. They bring the members of the Academy who are interested in the basic sciences into closer relationship with those members of the Academy whose interests are entirely clinical, and this is to the mutual good of both. They allow also for the total representation of neurology within the Academy. The parameters have been broadened from a basically Middle Western biannual clinical society, and instead we see one of the world's largest, most active, most truly representative societies in the field of neurology.

Any organization with this phenomenal growth must undoubtedly have had growing pains. Yet the growing pains of the Academy have been few and only intramural, dealing with our own deliberations. In our extramural activities, we have had no serious difficulty. Most important has been the development of our relations with the American Neurological Association. Now the American Neurological Association is the senior society. It is the prestige society. It is the Phi Beta Kappa of American neurology. I believe it is best to represent the American Neurological Association as the U. S. Senate and the American Academy of Neurology as the House of Representatives. The American Academy of Neurology is, by and large, somewhat younger, somewhat noisier, more broadly representative, while the American Neurological Association is older, somewhat more discreet, more select. The first one wisely to be apprised of this relationship was Dr. A. R. Vonderahe of Cincinnati, who judiciously pointed this out to several key members of the Academy and who served so well on our Board of Trustees. To him belongs the credit for keeping the record straight between the American Neurological Association and the American Academy of Neurology. Every young medical student going into his internship with an eye on neurology should expect to join the Academy of Neurology as a

junior member on the first day of his residency and hope, as he matures, to become a fellow of the Academy and a member of the American Neurological Association.

From time to time, individual members of the Academy have wondered about the relationship of the American Academy of Neurology to the American Board of Psychiatry and Neurology. The Academy has had, for the past two years, a committee of the Board of Trustees for liaison with the American Board of Psychiatry and Neurology. But there is much better evidence of the close relationship between the American Academy of Neurology and the American Board of Psychiatry and Neurology. At the present moment, one member of the Board of Trustees is a director of the Board, the editor of the Journal, and the immediate past president of the American Board. The first president of the Academy is now a director of the Board, and your own president serves as vice-president on the Board, so the American Academy of Neurology is certainly well represented on the Board!

The Academy has also a strong role in the public relations for neurology. The meetings and particularly the special courses, and most particularly the special course for general practitioners, plus the availability of the publication *Neurology*, have brought neurology before the practicing physicians and family doctors of this country.

The voluntary health organizations have become increasingly more prominent during the exact period of growth of the Academy. The Academy realistically was aware of this and early appointed liaison committees to work with the voluntary health organizations. Working together with the voluntary health organizations, the Academy did much to aid in the formation of the National Institute of Neurological Diseases and Blindness of NIH and has cooperated closely with Public Health Service officials in aiding neurology and the sister specialties. Indeed, this aid has gone into the field of medical education in general as far as neurology is concerned, and the Academy officials have been active in the conferences supported by the NINDB on neurologic education. The Academy has not been guilty of appealing directly to the laymen but has always been dignified and highly ethical in its approach. It has worked with government agencies, voluntary health organizations, with medical societies in the best interests of all concerned. The Academy has accomplished this through the leadership and work, particularly, of two past presidents—Drs. Fabing and Baker—and your next president, Dr. Rose.

The officers of the Academy, during the past eleven years, have been fully cognizant that in order to build strongly for the future, great attention must be spent on development in the present. When the Academy began its existence, one of the chief problems was the relative paucity of training places and of trainees in the field of neurology. We have all witnessed a remarkable upsurge of training centers and of numbers of trainees, but I assure you, this has not been accidental. Your vice-president, A. L. Sahs, serving as the chairman of the Training Grants Committee of NINDB, has devoted himself to the task and indeed has spent an appreciable proportion of his time in the past several years in travel around the country, visiting training centers and trying to help them.

The accomplishments of the Academy, then, have been to improve the quality of clinical neurology, to strengthen the ties between clinical and basic neurology, to make the medical public more aware of the role of neurology, to spearhead the drive for increasing the number and quality of physicians educated in the field of neurologic sciences, and to improve undergraduate teaching, graduate teaching, and even continuation of education. What could be more holistic?

We find that our Academy was instrumental in the formation of the World Federation of Neurology and our second president, Dr. Pearce Bailey, serves as the new Secretary General of the World Federation of Neurology. He has helped embark us on a planetary concept. I believe the Academy only awaits Operation Moon Shot for its final stage. We must not become provincial and feel that neurology is the heritage of the Americans or of the American Academy. Of this, I am sure, all of us are aware. Our relationship in the World Federation and in the First International Congress of Neurology has proven this. Other relationships with our fellow scientists in the Soviet Union are cordial. Recently a delega-

tion comprised of members of the Academy and under the Chairmanship of your President visited the Soviet Union as an official governmental mission sponsored by the NINDB. The number of scientists engaged in neurologic research in the U.S.S.R. is impressive and the quality of the work is excellent. The Soviet scientists in turn visited our own laboratories in this country, and it is hoped that, with international cordial relationships such as these between scientists, neurology can contribute toward world peace and understanding. One point which seemed to me particularly impressive in the Soviet Union is that in the institutes the various subdisciplines are not phased out as so often happens in our country. Let me explain: In an institute of neurology, for example, there will be a section on descriptive anatomy as well as sections of physiology and of chemistry. Oftentimes in this country we are inclined to jump on the band wagon of the newest discipline and discard an older one. This does not leave us in the best position for cross-fertilization between subdisciplines.

We can look with true pride on American neurology and the direction it has taken and the speed with which it is developing. Let us look for a few moments at the future of the Academy. An organization with a small beginning and a rapid take-off like this, with its tremendous thrust upward, should certainly prosper and continue to grow. The membership has doubled in the past three years. It is not difficult to predict a bright, promising future for an organization like this, but I would be remiss as your President if I did not point out to you some of the pitfalls for the future. We have only to fear complacency and the willingness to accept what we have without continuing the striving for improvement.

We must continue to train only the best men available, and we must continue to make progress in our training procedures. We must always remember that the residencies exist for the resident and not the resident for us. In many aspects of graduate medical education, the resident may become merely another pair of hands to help the chief. This is not the tradition in neurology, and all of us who are engaged in teaching know full well that the more residents on the service, the more faculty is necessary. The need for training in clinical neurology is as urgent as it ever was—despite the increase in training centers and number of residents—and the dearth of neurologists remains as great now as it ever was. This is because so many of the trainees, on completing their education, turn toward research. We are in no danger of oversaturation. The government services, both military and nonmilitary, are in desperate need of neurologists, and one of these services could absorb over 30 clinical neurologists tomorrow if they were available. The universities still are in desperate need of neurologists. There are still institutions clamoring for their first neurologist, and one neurologist begets the need for many more.

The research potential is far from saturated. Indeed, the research potential in this field among finite things is the nearest one can come to infinite. And were the teaching and government service places and were the research potentials all satiated, there is still the matter of service which has not even been lightly affected. Where are the neurologists in Springfield, Massachusetts; York, Pennsylvania; Norfolk, Virginia; Springfield, Illinois; and Tacoma, Washington? These are moderately sized cities without universities and chosen at random. You can name many more than I can, yet our citizens in these areas are entitled to the advances made in the neurologic field. The mission of the Academy is not accomplished—we are in no danger of oversaturation. This occurs in some of our sister specialties, and at this point I would like to indicate to you that the Board of Trustees and officers of the American Academy of Neurology have always had a careful sense of timing. They have not gone on record in drives to make the public more conscious of the public need for neurologists without at the same time having stepped up training so that the output of programs could be somewhat commensurate with the demands raised.

We have touched lightly upon research. During this period of the Academy development, great increase in research efforts in the field of neurology has occurred. You can measure this increase by many yardsticks. One can use the amount of money spent by the United States Public Health Service and see this increase from $120,000 in 1952 to $18 million in the present year. You can measure it by the

quality and quantity of papers read before the Academy and other scientific societies. You can measure it by the number of members of the Academy and other neurologic organizations serving in research posts. It is important for us in our research efforts to be constantly aware that research in one specific area is dependent upon research in another. We barely realize that, had it not been for DeForest and the triode tube, electroencephalography as we understand it today would be impossible. Likewise, the enzyme studies in the spinal fluid would not be feasible were it not for the spectrophotometer. Each of us must continue to be alert for developments in contiguous and sometimes even remote fields of science, so that we may incorporate these innovations into our own research.* A neurologist has, within his scope, the aspects of many basic sciences—anatomy, physiology, chemistry, pharmacology, and pathology—and may devote his research interest to any single one or combination of these. This is the great appeal of neurology. This is what makes it so different from other medical specialties. Some professors of internal medicine have difficulty understanding this concept, but how glaring the difference is when one compares neurology, including neuroanatomy, neurophysiology, neuropathology, neurochemistry, and neuropharmacology with, say, cardiology or diabetes and their relationship to the basic sciences.

One of the great pitfalls is that we may become complacent and decide that these achievements and advances are our heritage, that they have come to us as our just due, and forget that they are the fruits of hard labor. It is important for us to work even harder along the lines whence our improvement has come.

It also is important for us to remember that the fate of the Academy is linked to the future of neurology. We must do all we can to strengthen neurology in the universities and to strengthen it as a separate discipline. Neurology must not be confused with the other disciplines of medicine, for to progress and grow it needs to be autonomous. We must strengthen training programs in clinical neurology not only in numbers but in quality and also in numbers and quality of trainees. In these ways and by increasing undergraduate teaching and research, we can hope to strengthen neurology in the educational sphere.

There is one danger for the Academy which is serious. Last year at the dinner of the Academy in Philadelphia, I paraphrased the founding of the Academy with the founding of our country, pointing out the collection of great men who had made the founding of our country possible and compared our first four presidents with Washington, Jefferson, Hamilton, Monroe, our editor of the Journal with Tom Paine, and so on. While this was in a light vein, beneath it was the fact that the Academy of Neurology came into a virile existence just as did our country, because there was a group of contemporaries highly interested, emotionally charged, and with the strength to do the job. Our country survived subsequent wars, subsequent internal dissension, and various trials and tribulations because there was a steady succession of men strong enough to carry on what the original leaders had set up.

After this glowing report on the Academy past, present, and future, I could with a steadier hand and with more peace of mind, turn over the gavel to my distinguished successor were there more evidence of support from future Abraham Lincolns and Theodore Roosevelts. There is work to be done. There is new leadership necessary. It is important for you, the younger members of the Academy, to begin the structuring of the world in which you will live. Thomas Jefferson owned 83 slaves when he signed the Declaration of Independence. Abraham Lincoln was a great liberal, and yet by modern standards he would be ultraconservative. There is a need for future change in leadership so as to keep *au courant*. No member of the Academy has refused to work before, no member has failed, and in turning over the presidency to my distinguished successor, Dr. Augustus Rose of Los Angeles, I am grateful to each and every member of this organization for all that you did to make my administration a successful one and ask only that you continue for my successor and that the younger members of the Academy exert themselves to the fullest.

*We must pay more attention to a broad research approach and avoid gaps in our program. May I point out to you the insufficient interest in industrial neurology, military neurology, and neuroendocrinology?

CASE REPORT

Intracranial chordoma

Remzi Demir, M.D., and A. Theodore Steegmann, M.D.

THIS CASE is reported to emphasize that intracranial chordomas are difficult to diagnose, even though improvements have been made in recent years in the technics used to visualize intracranial mass lesions.

The term, chordoma, introduced by Ribbert in 1894, refers to a rare tumor derived from the notocord. Although these tumors may occur at any level of the neuraxis, most are found at the sacrococcygeal level and within the cranial cavity. At the intracranial level, the tumors arise in the region of the clivus blumenbachii about 1 cm. posterior to the dorsum sellae. In about 2% of autopsies, the notochordal remnant can be found as a slimy excrescence which communicates through a small defect with the interior of the basisphenoid.[1] From this point, the tumor growth may project in different directions producing variations in the clinical picture. The direction of growth may be downward towards the pons and foramen magnum or upward and forward to invade the interpeduncular cistern, sella turcica, and sphenoid sinuses. The tumor may even invade the orbits. A case reported by Holzner[2] spread into the subarachnoid spaces to the spinal level and also into the ventricles. In our patient, severe compression of the pons and adjacent cranial nerves and extension forward into the sella turcica and sphenoid sinuses occurred. The cranial nerves at the mesencephalic level were subjected to long continued compression, and the nuclei showed interesting histologic changes.

CASE HISTORY

A 44-year-old man was admitted to the neurology service at the Kansas University Medical Center, November 2, 1955, because of double vision. His health had been good until eight weeks before admission when he complained of severe occipital headaches. These headaches continued for four weeks and subsided rapidly but were promptly followed by diplopia and internal rotation of the left eye. He had worked steadily as a painter and had been exposed to lead paints for many years but did not report colic or diarrhea.

On physical examination, he was a well developed, poorly nourished man free of demonstrable disease except in the central nervous system. His visual acuity and visual fields were unimpaired, but the right pupil reacted sluggishly to light. The fundi appeared normal. He had bilateral sixth nerve weakness with unsustained, horizontal nystagmus. A slight, left lower facial weakness was present, and the pharyngeal reflexes were sluggish. Tongue movements were performed clumsily. The deep reflexes were slightly more active in the extremities on the left, but Babinski's sign was not present. The patient was unsteady in standing and in carrying out the heel to knee test. No sensory changes were elicited.

Laboratory examination. No abnormalities were found in the routine examination of the blood, urine, and blood chemistry. No basophilic stippling of red blood cells was seen, and the urine test for lead disclosed negligible quantities. Blood acid phosphatase was 0.5 units, and alkaline phosphatase, 1.1 units. Bone marrow examination was normal. Blood serology was negative. The cerebrospinal fluid pressure was 170 mm.; cerebrospinal fluid and all tests were normal except total protein which was 54 mg. per 100 cc. Roentgenogram of the chest was normal, but the skull revealed erosion of the floor of the middle fossa. The roof of the sphenoid could not be identified, and,

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Fig. 1. Pneumoencephalogram to demonstrate (a) destruction of floor of sella turcica, (b) air above tumor mass, and (c) posterior extent of tumor in interpeduncular cistern.

on one side, the basilar foramina appeared wiped out. The anterior clinoids were practically gone or appeared as a shell. Biopsy by Dr. G. O. Proud of the nasopharynx of what appeared to be a smooth retropharyngeal mass on the right was reported as "adenoid tissue with mucus gland retention cyst." The patient was dismissed November 20, 1955, without a diagnosis, but a middle fossa tumor was considered the most probable diagnosis.

The day following dismissal, the patient became unable to walk, a left facial paresis was noted by his wife, and his speech became thick. He was readmitted to the hospital on November 24, 1955. A left lower facial weakness and a left hemiparesis, more pronounced in the arm, were present. No sensory changes were detected. He was not incontinent, but his urine contained 2+ albumin and was loaded with red blood cells and pus cells. The urinary excretion of 17-ketosteroids was 12 mg. per twenty-four hours—which is normal in our laboratory. Arteriography of the right common carotid was normal. A pneumoencephalogram was reported to show a soft tissue mass that extended from the cisterna chiasmatica back to the level of the cisterna interpeduncularis (Fig. 1). This was interpreted as evidence of a pharyngeal tumor that had invaded the middle fossa. A second biopsy of the nasopharynx failed to obtain tumor tissue. The patient was given a course of x-ray therapy without benefit. He was dismissed on February 15, 1956. At that time he was lethargic and had urinary incontinence but no papilledema. He died at home on December 5, 1956.

Autopsy. Only the brain was available for study.* A tumor lying at the base of the brain anterior to the pons had spread into the sella turcica, the paranasal sinuses, and the region of the nasopharynx. The sella turcica was almost completely destroyed, and no pituitary tissue could be recognized at autopsy.

The formalin-fixed brain weighed 1,513 gm., and the tumor mass lying anterior to the brain stem weighed 39.5 gm. Except for mild swelling, no gross abnormalities were visible, but the olfactory tracts were thin and ribbon-like (Fig. 2A). The tumor had compressed the pons and cerebral peduncles to a marked degree. The tumor was gray to white in color, varied in consistency, and measured 6 x 5 x 4 cm. in diameter. Sticky mucoid material appeared on the cut surface. The tumor mass was circumscribed and well encapsulated. It was composed of gelatinous masses or islands of gray tissue surrounded by translucent areas. Nerve fibers could be identified only in the capsule at the posterior end of the growth. The optic chiasm was compressed and pushed forward. The tumor completely covered and was densely adherent to the pons.

On removal of the tumor, a cavitation and severe compression of the pons on the right side could be seen. The basilar artery, although patent, had produced a longitudinal groove in the tumor (Fig. 2B). The fifth cranial nerves were compressed and greatly stretched on both sides. On the left, the fifth nerve became embedded in the tumor. The sixth cranial nerves were also stretched and compressed, and, except near its emergence from the inferior pons, the left sixth nerve could not be identified. The floor of the third ventricle was very thin, and the mammillary bodies were flattened and compressed posteriorly. All of the cranial nerves emerging in the cerebellopontile angle were flattened, especially on the right side. The third cranial nerves could not be identified on either side. The arteries of the circle of Willis were patent. A moderate degree of uncal herniation was seen. Coronal sections of the brain appeared normal, except for moderate ventricular dilation most pronounced in the third ventricle. Microscopically significant changes were found only near the brain stem and in areas adjacent to the tumor.

The histologic appearance of the tumor varied in different areas—depending on transformation of more solid regions (Fig. 3A) into area composed mostly of physaliferous cells, many of which had broken down to form cystlike areas filled with mucinous material (Fig. 3C). Islands of tumor cells, irregular in shape, containing round, ovoid hyperchromatic nuclei, can be seen. In such areas, the cytoplasm is solid in places but tends to become vacuolated (Figs. 3C and 3E). In other places, there are vacuolated spheroid cells containing multiple nuclei (Fig. 3B, arrow), or a single nucleus lying in loose mucinous tissue (Fig. 3C, arrow). In places, a thin capsule is present surrounding cystlike cavities. The tumor is relatively avascular. Periodic acid shift stains reveal deep red granules in the cells, most of which are digested by malt diastase and are considered to consist of glycogen (Fig. 3D). In Nissl stains, the mucoid material slows metachromatic properties. In decalcified sections taken from the region of the sphenoid bone and parasellar area, tumor cells can be seen surrounded by islands of bone. No difference in the tumor structure is seen in such areas. No cells can be identified as pituitary gland. Bundles of degenerated nerve fibers can be identified in the capsule of the tumor and in decalcified areas. Sections through the brain stem stained by the Luxol blue myelin sheath method exhibit severe compression of the pons forward so that part of the pons lies beneath the markedly compressed cerebral peduncles (Fig. 4A). It should be noted that the peduncles are not demyelinated. At this level, the aqueduct is flattened and, at a lower level, the fourth ventricle is also pushed upward (Fig. 4B). In this region, tumor tissue is seen invading the base of the pons near the midline, and the pyramidal tracts on the right side are severely demyelinated. This descending degeneration can be traced downward into the lower medulla shown in Figures 4C and 4D. The area of invasion in the pons is surrounded by proliferation of astroglia.

Other microscopic features of the case of interest are the changes observed in the cranial nerve nuclei. No degeneration in the medulla was present in the hypoglossal nuclei

*We are grateful to Joseph W. Parker, Jr., M.D., of Burlington, Kans., who removed the brain and sent it to the Neuropathological Laboratory.

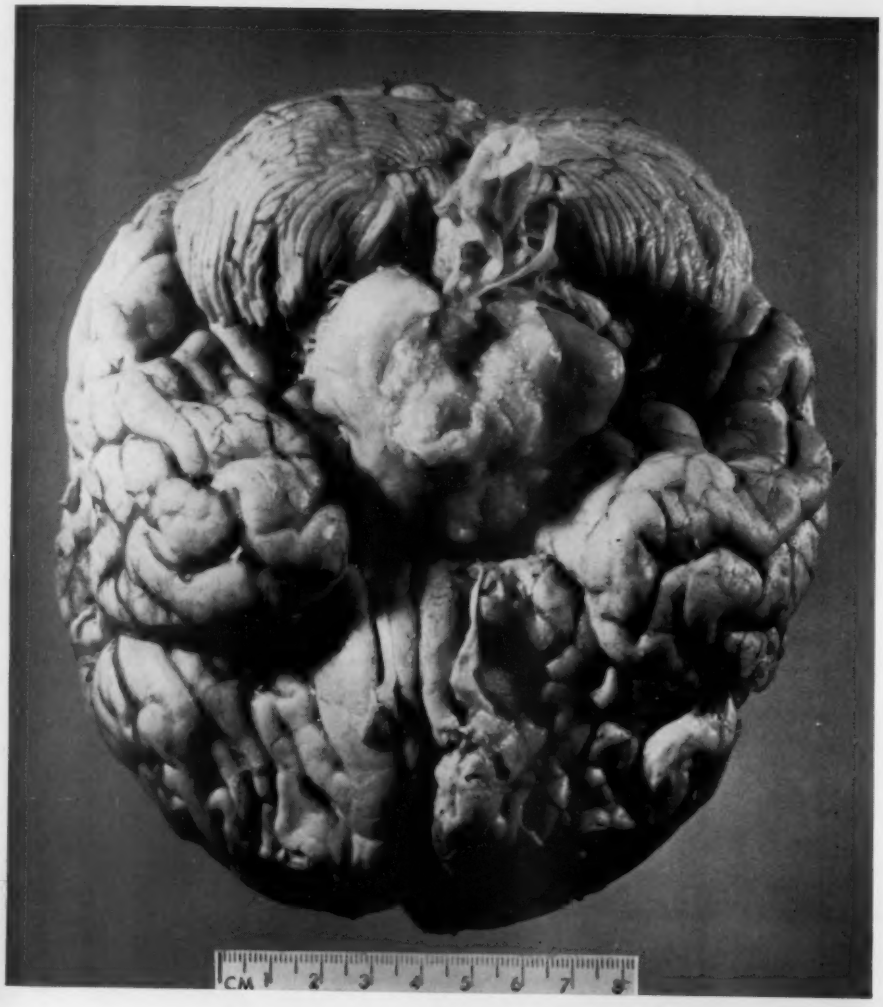

Fig. 2A (*Above*). Basilar view of brain with tumors in situ. Fig. 2B (*Right*). Appearance of pons after removal of tumor. Note depression on right and nonoccluded basilar artery. The optic nerves and chiasma are pushed forward.

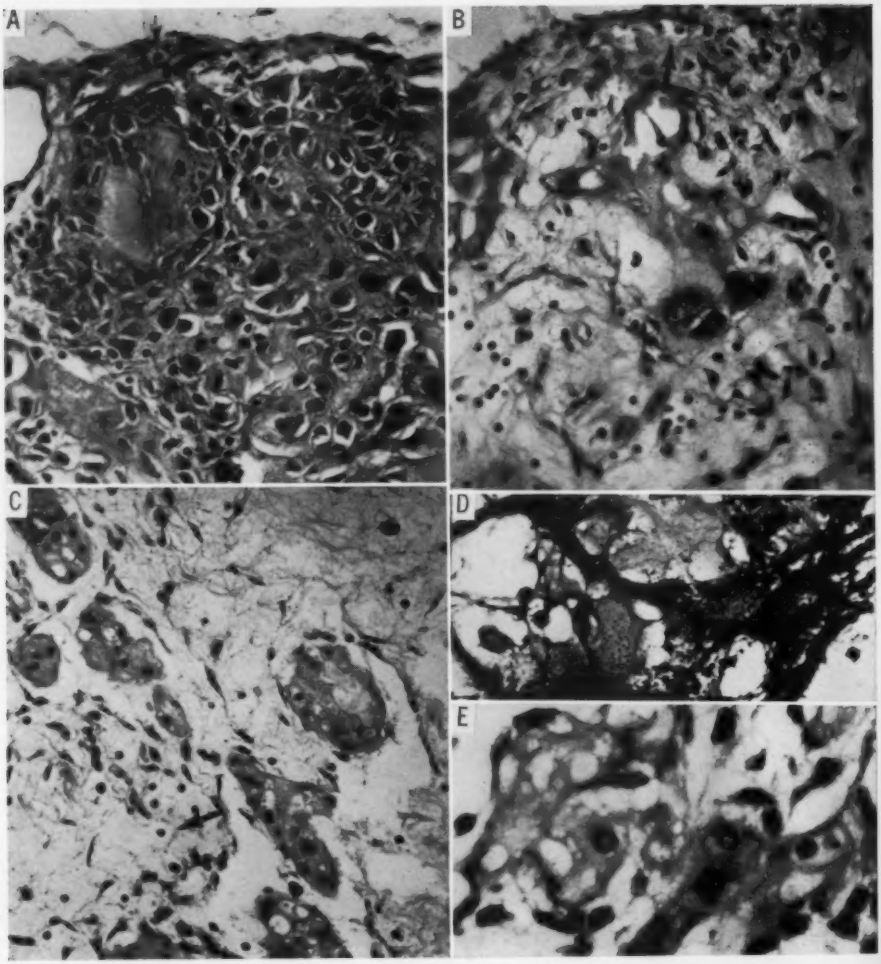

Fig. 3. Histology of tumor. (A) Solid area of tumor. H & E stain × 235. Spheroid cell (arrow). (B) Change of solid cells to physaliphorous cells. H & E stain × 235. (C) Islands of tumor cell lying in looser myxoid tissue. Spheroid cell (arrow). H & E stain × 235. (D) Glycogen granules in tumor cells. P.A.S. stain × 375. (E) Tumor cells to show vacuoles in cytoplasm. H & E stain. Enlarged from 193 ×

and in the ambiguus nuclei but, in the anterior brain stem at the superior colliculus level, the third nerve nuclei are greatly compressed. The cells of the Edinger-Westphal nucleus are flattened horizontally (Fig. 5, above) and lie above the dorsal portion of the lateral oculomotor nucleus. Many of the latter cells are likewise compressed and lie in a horizontal direction (Fig. 5, below). The number of cells in the oculomotor nuclei appear to be about equal in number on each side, but the motor ganglion cells show clumping of Nissl granules

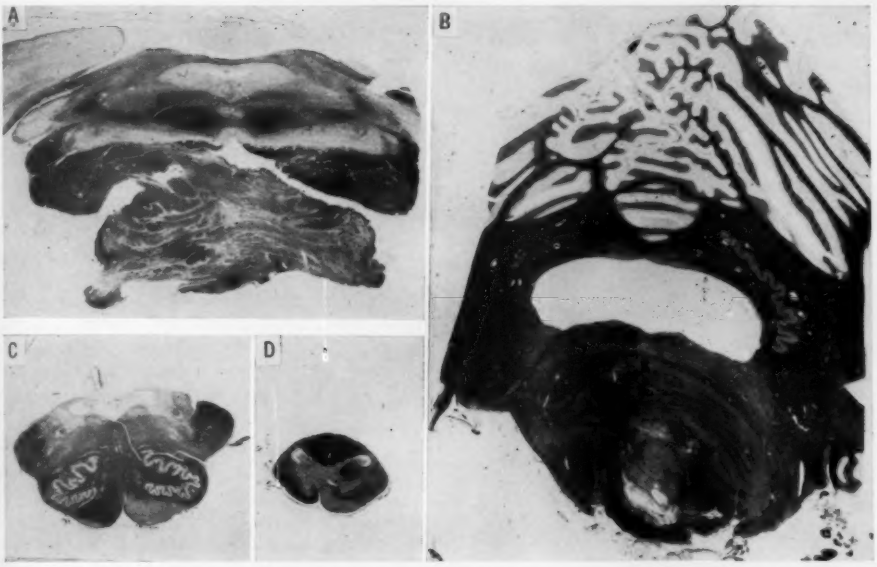

Fig. 4. (A) At level of superior colliculus. Note compression upward, flattening of aqueduct and underlying pons. Peduncles are not demyelinated. (B) Section through pons. Luxol blue stain. The right side (notch, arrow) is enlarged, partially demyelinated and contains tumor (arrow). (C) Section through medulla. Right pyramidal tract demyelinated. (D) Medulla at lower level. Corticospinal tract on right crossing to left side is demyelinated. All sections are magnified 2.5 times.

and, in some cells, chromatolysis and vacuolation of the cytoplasm. Some neurons contain an excess of lipoid pigment. Surprisingly little proliferation of fixed glial elements is seen. At the inferior pontile level, the nuclei of the abducent nerves show more pronounced degeneration with reduction in the number of cells, especially on the left side (Fig. 6). Here can be seen severe chromatolysis (Fig. 7A), shadow cell with vacuolation (Fig. 7B), clumping of Nissl granules and flattened cells (Figs. 7C and 7D).

The cerebellum shows some significant changes consisting of chromatolysis and increase of lipoid pigment in the Purkinje cells with loss of many. Proliferation of glial nuclei occurs, especially in the Bergmann layer. Paling of myelin fibers also is seen in the medullary substance of the hemispheres. In spite of gross herniation of the uncal gyri, no degeneration was found. The region of the hypothalamus exhibited cellular changes. The

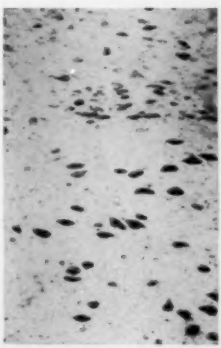

Fig. 5. Cells of third nerve nucleus. Cells of Edinger-Westphal nucleus above. Note horizontal arrangement from compression. Nissl stain × 95

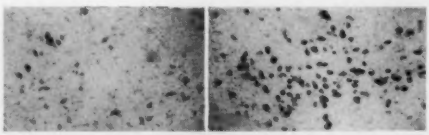

Fig. 6. Cells of sixth nerve nuclei to show comparison on each side. Note sparsity of cells on left side. Nissl stain × 60

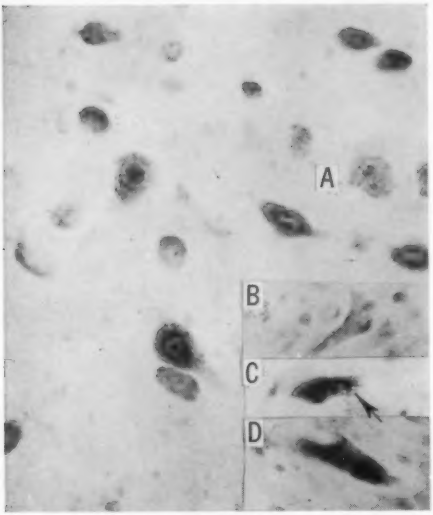

Fig. 7. Right sixth nerve nucleus. Ganglion cells show (*A*) chromatolysis, (*B*) shadow cell with vacuoles, (*C*) and (*D*) clumping of Nissl granules in flattened cells. Note nuclear cap (arrow). Nissl stain × 235

nucleus supraopticus showed some cell loss and chromatolysis. More severe degeneration was present in paraventricular nuclei which were not easily identified. Neuronophagia and pronounced subependymal gliosis were seen.

DISCUSSION

The tumor in this case arose from the clivus blumenbachii and spread upward and forward to invade the sella turcica and sphenoid sinuses. The pons was compressed backwards. Although the clinical symptomatology varies in different cases, depending on the direction of extension of the tumor mass, the clinical characteristics of intracranial chordomas emphasized by Bailey[1] are demonstrated here. They are a slow clinical course with late appearance or absence of intracranial hypertension; early appearance of cranial nerve palsies which may dominate the clinical picture; pyramidal tract or cerebellar signs produced by compression rather than invasion of the cerebral and cerebellar peduncles; and pain and stiffness of the neck resulting from extension of the tumor in the direction of the foramen magnum. All of these characteristics were present in this patient with the exception of pain and stiffness of the neck which was absent because the tumor mass did not invade the foramen magnum. It should be mentioned, however, that occipital headache was his initial complaint. The explanation of left hemiparesis and cerebellar ataxia is clarified by the degeneration of the cerebellar white matter and pyramidal tracts shown in the myelin sheath stains. This arose strictly at the pontile level. Of numerous diagnostic procedures carried out, changes in the roentgenogram of the skull were the first objective evidence of the lesion. Pneumoencephalography proved to be of additional value in visualization. Angiography gave no help in this case, but the technic has been reported to be successful.[3]

The value of roentgenography has been emphasized by others.[4,5] A chordoma should be suspected when bone destruction or a soft tissue mass is visualized in the sphenooccipital and hypophyseal areas in the midline—since most of these tumors arise in the region of the clivus. Therefore, a basilar view of the skull is very important. The dorsum sella is usually destroyed first and, after the tumor has invaded the sella, destruction of the posterior clinoids and hypophyseal floor follows. The anterior clinoids are eventually destroyed.[4] The soft tissue mass may sometimes be visualized by laminography. In our case, the pneumoencephalogram showed the best visualization. Failure to obtain tumor tissue by 2 nasal biopsies precluded a pathologic diagnosis but gave some support that the lesion was not primarily of nasopharyngeal origin.

At the present time, well over 500 chordomas have been reported. About 40% of these are intracranial. About 50% are found at the sacrococcygeal level. Of the intracranial chordomas, about half are found in the sphenooccipital region, and the remainder are about equally divided between the hypophyseal and nasopharyngeal regions.[4] The sphenooccipital chordomas constitute less than 0.5 per 1,000 intracranial tumors.[6] Approximately 5 to 7% of the chordomas appear in the cervical region.

Chordomas may occur at any age in either sex but are most common in the third and fourth decades. The early appearance of cranial nerve palsies is important in the natural

history of these tumors, and all of the cranial nerves—from the optic to the hypoglossal—may be involved. Diplopia is present in two-thirds of the patients and abducent nerve palsy in about half. Compression of the cerebral and cerebellar peduncles leads to cerebellar and pyramidal tract signs. The insidious onset and slowness of compression of neural structures frequently lead to death before the appearance of signs of intracranial hypertension. Headache is, however, a common symptom and cannot be explained by intracranial hypertension. Pituitary dysfunction causes amenorrhea, obesity, sterility, and loss of libido in some patients. If the tumor extends into the nasopharynx, nasal obstruction and a purulent discharge may occur. Cervical lymph adenopathy is rarely seen, but the tumor may invade the orbits and middle ear and even extend into the structures of the neck and regional veins. Variations depend upon the direction and extensiveness of local invasion.

Because of the tumor's inaccessible location, surgical removal is difficult, if not impossible, and recurrence after partial removal can be anticipated. Roentgen therapy is ordinarily not effective, but a small percentage of cases have shown a favorable palliative response.

The gross and microscopic appearance of the tumor in this patient is characteristic and similar to previously reported cases.[1,7,8] The transformation of solid cells into physaliphorous cells by the process of vacuolization with eventual extensive accumulation of mucinous material in the cytoplasm can be traced through its various stages. Special stains show that both glycogen and mucin accumulate in the tumor. Signs of malignancy in tumors indicated by mitotic figures and giant cell formation are not found in the chordomas, but their unfortunate location and invasive character explain the seriousness of these lesions. Chordomas do not metastasize in the ordinary meaning of the term but do spread within the subarachnoid spaces.

The retrograde changes found in the motor neurons of the oculomotor and abducent nuclei are interesting and resemble changes described by Brodal[9] in experimental animals. Brodal showed that axonal injury is not always followed by the axonal reaction seen commonly in the anterior horn cells of the spinal cord after peripheral nerve section or injury. Instead, the motor nerve cells show changes of a variable and quite different character. This was found to be true in cells of the inferior olive and brain stem motor cranial nerve nuclei. The cells showed disintegration of tigroid granules without nuclear displacement and swelling of the cells, and the cells later became atrophic. It would appear in this case that slow compression of the motor cranial nerves and their nuclei gave rise to degenerative changes of a very similar character. More studies are needed in man to confirm these observations. This may have clinical importance with regard to the regeneration of slowly compressed cranial motor nerves.

SUMMARY

A case of intracranial chordoma presenting typical clinical symptomatology is reported.

Pneumoencephalography and changes in the roentgenograms of the skull are the most useful aids in the diagnosis. Nasal biopsies failed to reveal tumor tissue on 2 occasions.

Surgical removal of the tumor is difficult or impossible and offers only palliative treatment. Radiation therapy is also of little value.

In this patient, the motor cranial nerves and their nuclei at the level of the pons and mesencephalon were subjected to long compression. Histopathologic changes in these nerve cells showed no evidence of the axonal reaction.

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Failure of amyotrophic lateral sclerosis to respond to intrathecal steroid and vitamin B_{12} therapy

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In 1955 and 1956 in Texas, a small number of patients with amyotrophic lateral sclerosis were treated with intrathecal water-soluble hydrocortisone and vitamin B_{12}.

The early results of this therapy seemed encouraging, and it was decided to give this treatment an intensive trial in Guam. Although this therapy was not successful, the experiment is reported here to demonstrate the relative ease of assessing such a therapy on Guam, our methods of selecting and evaluating patients, and the safety of the intrathecal injections.

BACKGROUND

During the past several years, numerous attempts have been made to use ACTH, cortisone, and hydrocortisone in the treatment of various chronic progressive neuromusclar disorders. The results of these clinical investigations have been most discouraging. However, the possibility exists that the failures have been due, in part, to the relatively high blood-brain barrier and, perhaps, also to an even higher blood–cerebrospinal fluid barrier to these substances.

In the latter part of 1954, the first of a series of new water-soluble derivatives of both cortisone and hydrocortisone became available for investigational use. It then seemed appropriate to administer these compounds by the intrathecal route, since they were readily diffusible in cerebrospinal fluid.

The first of these derivatives, cortisone disodium phosphate, was injected into the lumbar subarachnoid space of rhesus monkeys to determine whether any toxic reaction would result. A total of 10 mg. of this cortisone salt in 2 cc. of isotonic saline was instilled in each instance. When no deleterious effect was noted after ten days, it appeared safe to administer this compound to patients, particularly since an even greater reservoir of diluent would be present in the patients. Hydrocortisone sodium succinate (Solu-Cortef) was substituted for cortisone disodium phosphate in March 1955, when the latter was no longer available.

For many years, research workers and clinicians alike have sought clues to the causation of the inexorable progressive neuromuscular wasting associated with amyotrophic lateral sclerosis. Most physicians will agree that the disease process behaves in a way that suggests an underlying metabolic defect, but the nature of this defect is not understood. However, it is clear that the disturbance is dependent upon some peculiarity of motor neurons, which sets them apart from other cells of the central nervous system, so that they alone suffer from a slowly progressive degeneration. Unlike the clinical course of multiple sclerosis which is one of acute exacerbations with marked remissions, amyotrophic lateral sclerosis characteristically follows a continuously progressive trend to an eventual fatal outcome. There may be, however, apparent clinical "plateaus" and even slight improvement of short duration. For this reason, therapy in amyotrophic lateral sclerosis must be evaluated, remembering that it is most unrealistic to expect any return of function in neurons damaged beyond a certain undetermined limit.

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It does seem reasonable, however, to assume that as yet unaffected neurons might be protected and that partially involved cells might recover or be prevented from further deterioration by successful therapy.

As one further step, these water-soluble corticoids were injected intrathecally in victims of amyotrophic lateral sclerosis; vitamin B_{12} was combined with the injections from the outset. The latter was employed because of its reported effect in increasing the pentose nucleoprotein (PNA) content of anterior column cells in animals previously maintained on a diet deficient in folic acid, para-aminobenzoic acid, and vitamin B_{12}.[1] It also has been demonstrated that neuronolysis in sympathetic ganglion cells is diminished by the administration of vitamin B_{12}.[2] Motor neuronal degeneration, at least in part, must be due to or accompanied by disturbed protein metabolism, and many investigators support the concept that the nucleic acid content of a cell is indicative of the state of protein metabolism within the cell.[3] In addition, it has been shown that administration of cortisone increases the urinary excretion of vitamin B_{12}.[4] It seemed reasonable, therefore, to administer large doses of vitamin B_{12} to patients with neuronal disease who were receiving corticoids.

Initially, a series of 8 patients were treated in Houston by one of the authors (W.S.F.). After several months, the initial evaluation of this program revealed results that were encouraging, particularly in subjective improvement. For this reason, it was decided to give this therapy an intensive trial, and one of the authors (S.J.L.P.) agreed to undertake the evaluation in conjunction with the program of the Field Station, Epidemiology Branch, National Institute of Neurological Diseases and Blindness (NINDB) and the Guam Memorial Hospital. The selection of Guam, where the incidence of amyotrophic lateral sclerosis has been high, was based on several factors.[5–7] All clinicians who have worked on Guam and neuropathologists who have studied autopsy specimens from Guam agree that amyotrophic lateral sclerosis there is identical with the disease as observed elsewhere. The government of Guam is vitally interested in the study of this disease, and its Department of Medical Services cooperates actively with the NINDB in a program for observation and treatment of these patients. These organizations maintain a complete list of all known patients. This large number of patients (over 40 at any one time) and the ease with which one physician may study, treat, and evaluate such a group made Guam an ideal place for this study.

Administration of the drugs. Therapy was administered to the patients with amyotrophic lateral sclerosis on either an inpatient or outpatient basis. Patients who were still able to work were treated as outpatients, being given an injection once weekly on Saturday mornings, and were allowed to return home one hour after the therapy. All other patients were admitted to the hospital during the first week of each calender month and received a total of 4 daily injections during each admission. The drugs were administered intrathecally by lumbar puncture. Each 2-cc. injection contained 1,000 mg. of vitamin B_{12} and 50 mg. of hydrocortisone sodium succinate.

Each patient's temperature, pulse, blood pressure, and respiratory rate were determined on admission, and each was questioned generally as to his health and specifically concerning recent respiratory infections and skin rashes (scabies and impetigo are common on Guam). Intrathecal injections were not given to any patient until his fever was controlled, skin rash healing, and any cough subsiding.

Evaluation. The clinical status of each patient with respect to his neurologic disease was evaluated before the start of therapy. In addition, after five months and again at nine to ten months after the start of the therapy, an attempt was made to reexamine each patient. All patients were examined by one of us (S.J.L.P.) without reference to previous records. On occasion, other physicians examined the patients, but this was usually in consultation concerning other conditions.

A simple grading system was devised by the examiner and used to determine the patient's progress. Each patient's disease was subdivided into 4 categories of progressive muscular atrophy, lateral sclerosis, bulbar palsy, and pseudobulbar palsy. The severity of each category was graded using 0 (no involvement) through 4 (extreme involvement) as a scale. Characteristics of each grade are described. In particular, specific muscle testing of approxi-

mately 70 muscles on each side of the body from the head to the toes was performed at each test using a 6 value scale, 0 (absent) to 5 (normal), to evaluate muscle strength. This is a useful and accurate way of determining a patient's ability to perform certain tasks and a relatively objective manner of checking the patient's statement about his strength.

DATA

National origin. A total of 26 persons are included, all of whom were born in Guam. One patient was born of a native mother and a "stateside" father; both parents of all other patients were born in Guam.

Sex. A total of 8 females and 18 males were treated, a ratio of 1:2.25.

Age at onset. Age at onset of initial symptoms is as follows:

	Range (years)	*Mean (years)*	*Median (years)*
18 males	29 to 69	44	44
8 females	20 to 47	37	39
26 total	20 to 69	42	43

Duration of disease. Duration of symptoms from time of onset to initial therapy is as follows:

	Range (months)	*Mean (months)*	*Median (months)*
Male	4 to 74	27	19
Female	13 to 70	42	44
Total	4 to 74	32	33

Accuracy of diagnosis. The diagnosis in 24 patients was obvious and was based on a clinical history of a progressive degenerative disease of upper and lower motor neurons without evidence of sensory involvement. The diagnosis in one case was based on a progressive atrophic flaccid paralysis of the upper extremities with widespread muscle fasciculation. In only one case was the diagnosis of lateral sclerosis alone made.

Severity of disease. Symptoms or signs of progressive muscular atrophy were present at the time of initial therapy in 24 patients; of lateral sclerosis, in 23 patients; bulbar palsy, in 19 patients; and of pseudobulbar palsy, 14 patients. Only 2 patients had involvement in

GRADATION OF SEVERITY OF DISEASE

Progressive Muscular Atrophy (PMA): lower motor neuron spinal disease

0 = Absent signs or symptoms
1 = History of weakness, with fasciulations present and minimal weakness and atrophy of part of one extremity
2 = Fasciculations and moderate atrophy and weakness of two extremities with little loss of function
3 = Fasciculations and marked atrophy and weakness of two or more extremities with much loss of function
4 = Fasciculations and extreme atrophy and weakness of all extremities with almost complete loss of function and usually weak or absent deep tendon reflexes despite lateral sclerosis

Lateral Sclerosis (LS): upper motor neuron spinal disease

0 = Absent signs or symptoms
1 = History of stiffness of extremities (lower extremities usually) and/or slight symmetric increase in deep tendon reflex activity and/or easily exhausted Babinski or Hoffmann's sign
2 = Some difficulty in walking, particularly downhill, with very active deep tendon reflexes and easily elicited Babinski and Hoffmann reflexes with little alteration of muscle tone to passive movement
3 = Marked difficulty in walking and handling objects; frequent clonus on movement; extremely hyperactive or clonic deep tendon reflexes; easily elicited pathologic toe and finger reflexes; and moderate spasticity on passive movements
4 = Extreme spasticity, usually of lower extremities and trunk and often of the upper extremities, with clonus at several joints. This is not an easily defined stage because the muscular atrophy has usually progressed so far that the patient develops flaccid atrophy rather than spasticity

Bulbar Palsy (BP): lower motor neuron cranial nuclei disease

0 = No signs or symptoms
1 = Fasciculations of the tongue
2 = Fasciculations of the tongue, early atrophy of tongue, and slight weakness of gag reflex
3 = Fasciculations of the tongue and face, moderate atrophy of tongue, and apparent atrophy of pharyngeal and palatal muscles
4 = Severe atrophy of tongue, palate, and pharynx and loss of gag reflex

Pseudobulbar Palsy (PBP): upper motor neuron brain stem disease

0 = No signs or symptoms
1 = Slight difficulty in speech or swallowing by history or the presence of an easily exhausted palmomental reflex or sucking reflex
2 = Apparent difficulty in swallowing and speech, particularly the pronunciation of consonants; easily elicited palmomental and sucking reflexes; forced laughter; and easily porduced rage on occasions
3 = Severe difficulty in speech; occasional choking and nasal regurgitation; active palmomental and sucking reflexes; retracted tongue; and forced laughter and loss of temper
4 = Inability to speak; inability to swallow or to handle his own secretions; inability to protrude the tongue; and severe personality change with frequent forced laughter, frequent bouts of easily produced rage, often apparent loss of comprehension and communication

	Initials	Total number of injections	Numerical Gradation of Severity of Disease: Before Therapy PBP	BP	PMA	LS	Total	Five Months Later PBP	BP	PMA	LS	Total	Same Worse Dead Improved	Nine to Ten Months Later PBP	BP	PMA	LS	Total	Same Worse Dead Improved
1	J. S. A.	28	2	3	2	3	10	2	3	2	3	10	Same	2	2	2	3	9*	Improved
2	J. P. C.	24	0	3	2	3	8	1	2	2	3	8	Same	2	2	2	3	9	Worse
3	J. R. C.	8	3	3	1	3	10	–	–	–	–		Worse	4	4	4	4	16	Worse
4	V. T. D.	28	3	2	2	3	10	3	2	2	3	10	Same	3	3	3	3	12	Worse
5	R. R. G.	24	0	3	0	2	5	2	3	2	1	8	Worse	2	3	3	3	11	Worse
6	A. S. A. G.	6	2	3	3	4	12	–	–	–	–			–	–	–	–		
7	A. R. G.	24	1	2	2	1	6	1	2	3	1	7	Worse	1	2	3	1	7	Worse
8	F. N. I.	23	0	1	2	0	3	1	1	2	1	5	Worse	2	2	2	2	8	Worse
9	F. M. I.	1	2	2	3	4	11	–	–	–	–		Worse	3	3	3	4	13	Worse
10	J. A. M.	29	1	1	2	3	7	2	1	2	3	8	Worse	2	1	2	3	8	Worse
11	S. M. M.	25	0	0	2	0	2	0	0	2	0	2	Same	0	0	2	0	2	Same
12	J. R. Q.	32	1	0	3	3	7	1	0	3	3	7	Same	1	2	4	3	10	Worse
13	J. J. R.	26	0	1	1	2	4	0	1	1	2	4	Same	1	2	1	2	6	Worse
14	T. J. R.	4	1	2	4	3	10	Expired					Dead	Expired					Dead
15	J. R. R.	17	0	0	0	2	2	–	–	–	–		Same	0	0	0	2	2	Same
16	M. S. S.	16	0	0	2	1	3	1	0	2	1	4	Worse	1	0	2	1	4	Worse
17	N. S. S.	20	0	0	2	0	2	1	0	2	0	3	Worse	1	0	2	1	4	Worse
18	L. M. T.	4	3	3	3	3	12	–	–	–	–			–	–	–	–		
19	J. S. T.	32	3	3	2	3	11	3	3	2	3	11	Same	4	3	4	3	14	Worse
20	J. T. M.	24	0	2	1	1	4	–	–	–	–			Expired					Dead
21	D. B. Q.	20	0	3	3	3	9	–	–	–	–		Worse	3	3	3	3	12	Worse
22	J. S. N. C.	21	3	4	4	4	15	3	4	4	4	15	Same	Expired					Dead
23	J. S. A. R.	16	2	0	2	2	6	Expired					Dead	Expired					Dead
24	T. B. C.	20	0	3	3	3	9	3	3	4	3	13	Worse	Expired					Dead
25	F. A. A.	20	0	0	1	1	2	0	0	1	1	2	Same	0	0	2	1	3	Worse
26	G. C. H.	16	3	2	3	3	11	3	3	3	3	12	Worse	3	3	3	3	12	Worse

only 1 category; 4 patients had involvement in 2 types, and 12 patients had symptoms or signs of all 4 categories.

Completeness of therapy. All 26 patients received one or more injections of the drugs under study. All but 5 of the patients received at least 16 injections. Reasons for discontinuing therapy were as follows (see table):

Case 3. Her husband could not accompany her to the hospital and also care for the children at home.

Case 6. Her children were unhappy because she cried so much in the strange environment of the hospital.

Case 9. The patient did not want any more lumbar punctures.

Case 14. This man died of a respiratory infection two weeks after the initial series without seeking medical care for his acute illness.

Case 18. This lady never trusted physicians, preferred native herb doctors.

Of these 5 patients, 4 are females. The strong desire to get well in order to support their families was a big factor in the men's 100% cooperativeness, despite the discomfort of the therapy. Only 50% of the women completed any prolonged course of therapy.

Results. A total of 21 patients each received at least 16 intrathecal injections of B_{12} and hydrocortisone.

Within *five months* after the initiation of therapy, 8 of these patients were worse, 1 had died, and 10 were unchanged; 2 were not evaluated because they hed resumed herb therapy and did not want to come to the hospital.

At the end of *nine to ten months* of observation, 1 patient had improved slightly and 2 were in the same condition, but 14 had become more severely affected and 4 had died.

The 1 patient who had improved after nine to ten months was examined three months later. His disease had again progressed to a stage as severe as at the initiation of therapy.

No records of the number of headaches or of traumatic punctures were kept, but these did not seem excessive. There were no acute complications requiring hospital observation

following any of the 517 intrathecal injections, with the exception of 1 patient who had only pain and point tenderness at the site of lumbar puncture for four days after an injection.

Autopsies were performed on 4 of the 6 patients who expired. The unique change noted was the presence grossly of dense adhesions of the spinal dura to the anterior and posterior walls of the vertebral column in the region of the injections. No such adhesions were noted within the dura. Microscopically there has been no evidence of arachnoiditis. The gross pathologic diagnosis in each case was amyothrophic lateral sclerosis. Detailed neuropathologic studies will be reported later.

DISCUSSION

Experimental therapy for the treatment of amyotrophic lateral sclerosis is difficult to undertake because the disease is rather uncommon in the United States and any one physician would have little opportunity to examine a large group of patients in a short period of time. It was decided to evaluate the therapy under discussion on Guam because of the high incidence of the disease and the existence of a research unit of the NINDB on the island. To determine progression or change in a patient's condition is sometimes difficult; to determine the rate of change is even more difficult, and no attempt has been made to do this. The success or failure of this therapy was to depend upon its ability to halt the progress of the disease; in this it failed.

Repeated lumbar punctures are not responsible for any acute problems, but their effect is of interest academically. The medication was not harmful as evidenced by the absence of reaction within the subarachnoid space. The dense extradural adhesions probably represent a reaction to bleeding produced by the introduction of the needle rather than any inflammatory reaction to the drugs.

The 2 patients who showed no progression of illness during the study period were a man with progressive muscular atrophy only and another man with lateral sclerosis only. It is well known that occasionally patients who develop only one form of motor neuron disease may live for many years before progressing or developing other forms of the disease. It was observed here, as has been previously documented, that patients with any or all forms reach plateaus at which they may remain for several months and may even appear to improve slightly before progression.

SUMMARY

Experimental therapy of amyotrophic lateral sclerosis was started in 26 patients. This treatment consisted of 4 intrathecal injections per month of vitamin B_{12}, 1,000 mg., and water-soluble hydrocortisone, 50 mg. Of the patients, 21 received 16 or more such injections. Of the 21 patients, 18 became more severely affected or died, while 2 patients remained unchanged and 1 person improved slightly. The improvement in the latter patient was short-lived, and the patient's disease progressed again by the twelfth month.

This investigative project is reported to show the failure of another therapy for amyotrophic lateral sclerosis, the methods used in selecting patients and evaluating the effect of therapy, and, incidentally, the absence of any significant clinical complications of intrathecal injections of vitamin B_{12} and water-soluble hydrocortisone.

The authors wish to express their appreciation to Dr. Leonard T. Kurland, Chief, Epidemiology Branch, National Institute of Neurological Diseases and Blindness, for his help in making this study possible and for his editorial assistance.

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Glossopharyngeal neuralgia associated with cardiac arrest and hypersecretion from the ipsilateral parotid gland

K. Kjellin, M.D., R. Müller, M.D., and L. Widén, M.D.

In 1926, Harris[1] was the first to report cases of the cryptogenic type of glossopharyngeal neuralgia. Since then, approximately 50 cases have been published. In a few instances, special syndromes have been described.

Hesse[2] reported that both glossopharyngeal and trigeminal neuralgia occurred in the same individual with hypersecretion from the parotid gland on the affected side during attacks. Riley and associates[3] were the first to report cases of glossopharyngeal neuralgia with cardiac arrest. Ray and Stewart[4] reported a similar case which was cured by ninth nerve section and suggested that atropine might have prevented the cardiac arrest. This suggestion was later demonstrated by Richburg and Kern.[5] Cases of glossopharyngeal neuralgia with cardiac arrest have also been reported by Roulhac and Levy[6] and White and Sweet.[7] In 1943, Browder (cited by Ray and Stewart[4]) performed intracranial section of the glossopharyngeal nerve in a patient of this type with complete relief of all symptoms.

The following report describes a patient with glossopharyngeal neuralgia accompanied by cardiac arrest and hypersecretion from the ipsilateral parotid gland.

CASE REPORT

The patient was a 50-year-old caretaker who had had attacks of facial pain for the past five years which were often accompanied by loss of consciousness. The attacks occurred over a period of three to four weeks at one- to two-year intervals. He had been treated for these symptoms at several hospitals and his condition had been diagnosed as psychomotor-type epilepsy or facial, probably trigeminal, neuralgia.

The reappearance of pain in January 1958 led to his admission to the Neurological Clinic of Serafimerlasarettet. At this time, it was discovered that he had no pulse during the syncopal attacks.

Each attack began with an intense, lancinating pain in the posterior portion of the soft palate and the throat on the left side which radiated to the front of the ear and the angle of the lower jaw. Simultaneously, the patient noticed that saliva collected in his left cheek. The pain did not radiate into the jaws, down the neck, or into the ear. Sometimes the pain reached a climax after a few seconds, sometimes only after two to three minutes. When the pain was most intense, the patient felt dazed and sometimes lost consciousness. According to his relatives, loss of consciousness, which lasted from a few seconds up to half a minute, was not accompanied by muscular jerks. He had never bitten his tongue nor had he ever been incontinent. He had never had an attack of syncope without preceding pain.

The onset of each period of attacks occurred in conjunction with an infection of the upper respiratory passages. During these periods, he had an average of 5 attacks during a twenty-four-hour period but the number ranged from 0 to 50. Approximately half of the attacks were accompanied by syncope. He seldom had more than 2 attacks in one hour, and, generally, a free interval of at least two hours followed. The attacks would also occur at night. At the beginning of a period of attacks, the pain was relatively mild and less frequently associated with syncope.

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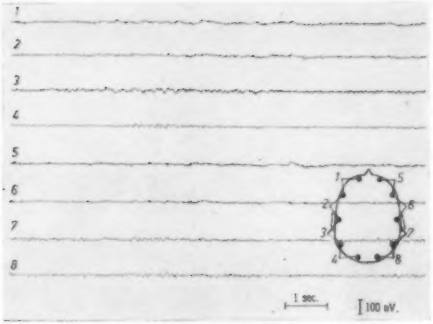

Fig. 1. Electroencephalogram recorded during a free interval, showing a slight focal abnormality in the left anterior temporal lobe.

Swallowing brought on the paroxysms more often than any other activity. Chewing alone had no effect. Food and liquids with a strong bitter, salty, or acid taste induced the attacks, but never anything sweet. Lemon especially caused the paroxysms and was avoided by the patient during attack periods. Yawning also precipitated attacks. Movements of the face—in talking, laughing, and grimacing—touching the face and gums as in shaving, brushing of the teeth, and so on—did not induce the pain.

The susceptibility to attacks showed considerable variation—even from hour to hour—and was reflected in the large variation in the frequency of the attacks.

Examination. Physical and neurologic examination revealed no abnormality. Otorhinolaryngoscopic examination was negative. The electrocardiograms at rest and after exercise were normal. No evidence was found of orthostatic hypotension. Massage over the carotid sinus on both sides for a period of fifteen seconds produced no significant slowing of the pulse. Roentgenograms of the skull, ears, sinus, esophagus, lungs, and heart, films of the act of swallowing, and the pneumoencephalogram showed normal conditions. The cerebrospinal fluid was normal. Wassermann reaction was negative in the blood and cerebrospinal fluid.

Description of attacks. During hospitalization, several attacks were observed. At the onset of an attack, the patient groaned, his face became contorted, and he made smacking and chewing movements and rubbed the painful area on the face. The pain then subsided abruptly or else he collapsed, became unresponsive, and exhibited mild, generalized muscular jerks. Unconsciousness lasted for fifteen to twenty seconds and, occasionally, up to forty

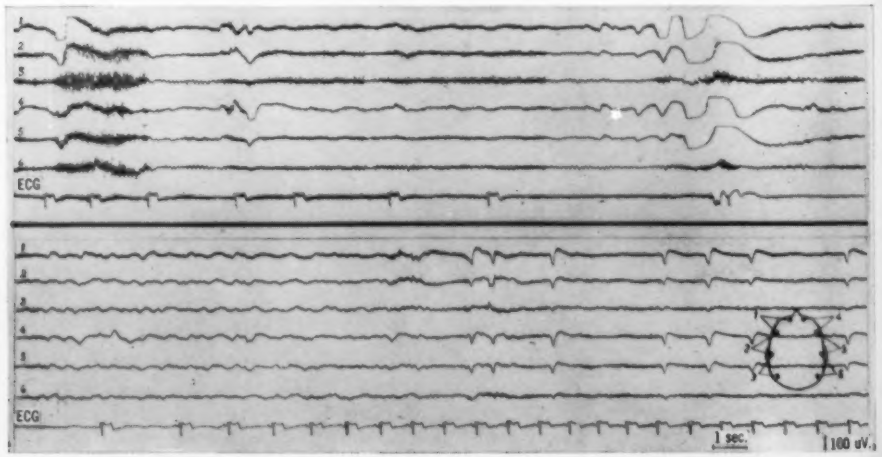

Fig. 2. Simultaneous records of the electroencephalogram and electrocardiogram during an attack accompanied by syncope. At the beginning of the record, bradycardia has already started. Toward the end of the period of cardiac arrest, bilaterally synchronous slow waves appear in the electroencephalogram.

seconds. In the attacks without syncope, he generally had bradycardia which, in the attacks with syncope, progressed to complete asystole lasting for several seconds. This was followed by occasional irregular heart beats, and, then, bradycardia before pulse rate returned to normal.

Trigger zones. Examination of the mouth, throat, larynx, external auditory canal, and the tympanic membrane revealed 2 distinct, small areas from which an attack could be precipitated: one in the upper part of the supratonsillar fossa on the left side (rubbing with a cotton applicator, nipping with forceps) and one at the entrance of the bony part of the external auditory canal (rubbing with a cotton applicator).

Catheterization of the eustachian tube and syringing of the left ear with cold water failed to induce an attack. A few drops of lemon juice or quinine solution applied to the supratonsillar fossa frequently evoked a momentary attack. Application of these solutions in other parts of the mouth and throat evoked a paroxysm only if the patient, with his tongue, shifted the solution to the trigger zone. Following topical anesthetization of the left tonsillar sinus with lidocaine (Xylocaine), an attack could not be evoked from the trigger zone in the left supratonsillar fossa and the patient could chew a slice of lemon without any discomfort.

Electroencephalographic studies. During a free interval, the electroencephalogram showed a mild focal abnormality in the left anterior temporal region (Fig. 1). During an attack accompanied by syncope, the record showed bilaterally synchronous, slow, irregular waves (Fig. 2). These waves appeared several seconds after the commencement of the bradycardia and usually not until the interval between heart beats exceeded eight seconds. Simultaneously, the patient became limp and unresponsive. The abnormal discharges in the electroencephalogram were obviously secondary to the circulatory failure and, accordingly, not the primary cause of the clinical seizure. The slow waves disappeared within a few seconds after the pulse rate had returned to normal. The duration of the syncope appeared to parallel the duration of the electroencephalographic changes.

Electrocardiographic, pneumographic, and blood pressure records before and after administration of atropine. Figure 3 shows simultaneous records of the electrocardiogram (Lead I), respiratory rate, and blood pressure (measured in the right brachial artery) during spontaneous seizures before and after intravenous administration of 1 mg. of atropine. The first attack was accompanied by cardiac arrest, a severe fall in blood pressure, and syncope. The fall in blood pressure coincided with the bradycardia, which preceded the asystole. This was followed after ten to fifteen seconds by a nodal rhythm of low frequency for ten to twenty seconds and, then, return of normal sinus rhythm. During the attack after atropinization, only a slight bradycardia and a correspondingly insignificant fall in blood pressure occurred.

Parotid secretion. Quantitative measurement of the parotid secretion was done with a photoelectric sialometer (Diamant,[8] modification after Krasnogorski). Figure 4 shows the secretion from the right and left parotid glands during a spontaneous attack.

Drug effects. Intravenous administration of 0.5 to 1 mg. of atropine prevented the syncope; only a moderate bradycardia occurred during the attacks of pain. Atropinization also diminished the intensity of the pain. During hospitalization the patient was given 2 cg. of belladonna extract (1.5% alkaloids) 3 times daily which completely abolished the syncopal attacks and also diminished the intensity of the pain. Intravenous administration of 250 mg. of Dilantin had little, if any, effect; 100 mg. of Dilantin administered orally 4 to 5 times a day and intravenous administration of 190 mg. of Xylocaine were completely ineffective.

Operation. Intracranial section of the glossopharyngeal nerve was performed by Dr. L. Herlin after atropinization. The vagal nerve was left intact. No lesion was observed in the area exposed. Since the surgeon preferred to operate under general anesthesia, it was not possible to determine by stimulation the distribution of pain.

Postoperative follow-up examination. At examination two months after operation, the patient stated that he had had no return of the earlier symptoms. Sensibility to pain and touch in his mouth, throat, and external auditory canal was normal. Despite repeated attempts,

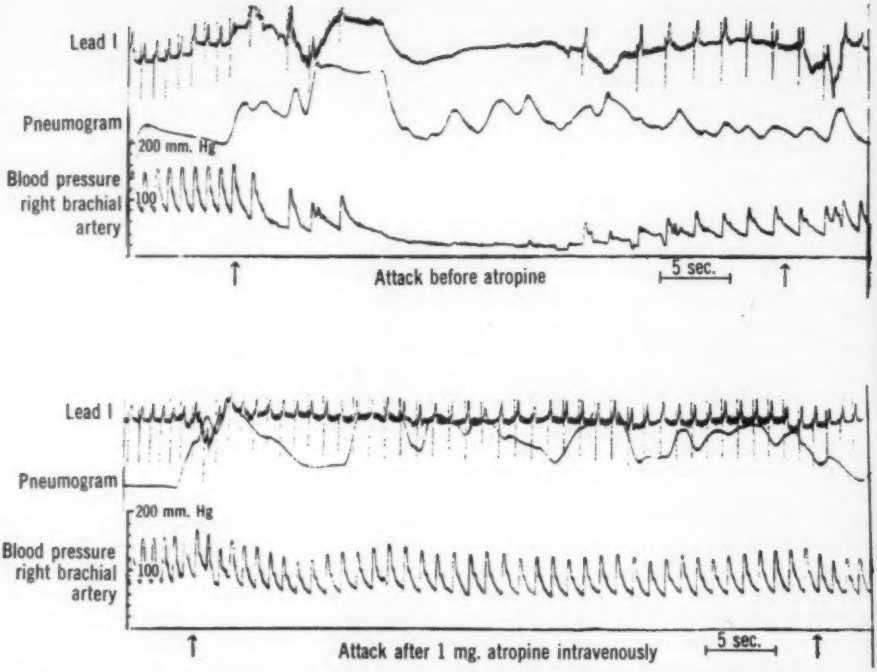

Fig. 3. Simultaneous records of the electrocardiogram (Lead I), respiration, and blood pressure (measured in the right brachial artery) during a spontaneous attack (A) before, and (B) after, the intravenous administration of 1 mg. of atropine. The first arrow denotes onset of the attack and the second arrow, the return of consciousness.

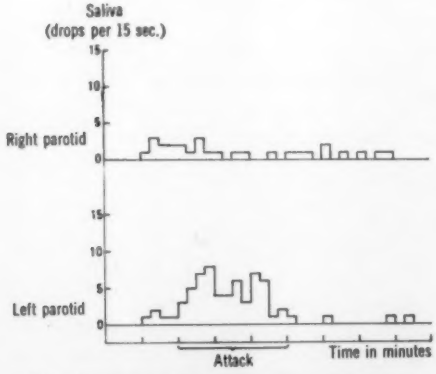

Fig. 4. Diagram of the secretion from the right and left parotid glands during a spontaneous attack determined with a photoelectric sialometer.

stimulation of the previous trigger zones failed to provoke the earlier pain. The normal cough reflex could not be evoked on mechanical stimulation of the left auditory canal. The electroencephalogram was normal. Sialometric investigation of the parotid function showed that lemon produced profuse secretion from the right parotid gland, while secretion from the left parotid gland was very scanty.

DISCUSSION

The complete syndrome in patients with glossopharyngeal neuralgia who have attacks of pain, bradycardia which sometimes progresses to cardiac arrest, and hypersecretion from the ipsilateral parotid gland does not appear to have been described earlier. All the components of the attack were very closely related in time.

As illustrated by this case history, the attacks of unconsciousness may be misinterpreted as epilepsy. Since, in these patients, loss of consciousness is always preceded by severe facial pain, this error can usually be avoided. Pain as an epileptic aura is extremely rare and would seem, like the pain which occasionally can be evoked by cortical stimulation,[9] to be mild.

In our patient, the electroencephalogram showed a slight focal abnormality in the left anterior temporal lobe on some, but not all, occasions. Therefore it may be questioned whether the cardiac dysrhythmia was not after all secondary to an epileptic discharge somewhere in the rhinencephalic structures of the temporal lobe. That mild disorders of cardiac rhythm occur in patients with temporal lobe epilepsy is well known.[9,10]

Phizackerley and associates[11] reported a case which they consider provides "clinical evidence for epileptic discharge from one temporal lobe firing into vagal autonomic pathways to produce cardiac arrest." In this case, however, no electroencephalographic recording was done during attacks. In our case, repeated recordings during the attacks showed that the electroencephalographic changes (bilaterally synchronous slow waves) were secondary to the bradycardia and cardiac arrest. The character of the electroencephalographic changes during the attacks and the time relations between cardiac dysrhythmia, disturbance of consciousness, and electroencephalographic changes agree with the reports of Gastaut and his associates[12,13] in a series of papers on the electroencephalogram and reflex vasovagal syncope and with our own observations in a few cases of carotid sinus syndrome.

The most plausible explanation for the complete syndrome would seem to be the presence of an irritative lesion somewhere in the peripheral course of the glossopharyngeal nerve where the nerve travels with the nerve of Hering.[7] Such lesions have been studied in experiments on mammalian nerves[14] and can be produced by dividing the nerve, by light pressure, or, as in intact human nerves, by ischemia.[15] As shown by Granit, Leksell, and Skoglund,[16] impulses which travel through such an injury zone—an artificial synapse—can excite neighboring inactive fibers. In this manner, bursts of impulses in the glossopharyngeal sensory fibers may activate the sinus nerve, of which the reflex effect would be a slowing of the pulse. The increased secretion from the parotid gland would also seem to be a reflex effect, since secretion ceased as soon as the glossopharyngeal nerve was divided. That artificial synapses may indeed be of clinical significance has been shown earlier in electrophysiologic studies in patients with hemifacial spasm.[17]

Of interest in the present case is the variations in the susceptibility to attacks, a phenomenon that is well known in trigeminal neuralgia. The pain gradually reached a climax and then rapidly subsided, or else syncope occurred. In trigeminal neuralgia, however, the pain pattern would generally seem to be the exact opposite.[18]

The trigger zone in the external auditory canal and the postoperative absence of the cough reflex on mechanical stimulation support the view of Hunt[19] and others that the glossopharyngeal nerve innervates the external auditory canal.

Worthy of note is the postoperative absence of sensory deficit in the oral cavity and the throat, an observation that has been made by several earlier authors.[5]

Atropine not only abolished the syncopal attacks, but also diminished the intensity of the pain. This latter observation was earlier made by White and Sweet,[7] while Richburg and Kern[5] reported that the pain was unaffected by atropine.

SUMMARY

A description is given of a patient with glossopharyngeal neuralgia associated with bradycardia which sometimes progressed to cardiac arrest and hypersecretion from the ipsilateral parotid gland.

Intracranial section of the ninth nerve completely relieved all symptoms.

ACKNOWLEDGMENT

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Infectious neuronitis (Guillain-Barré syndrome) in children

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Francis R. Dion, M.D., and Haddow M. Keith, M.D.

GUILLAIN, BARRE, and STROHL,[1] in 1916, delineated a syndrome characterized by progressive muscular weakness, sensory disturbances, tenderness of muscles, and albuminocytologic dissociation in the cerebrospinal fluid. Earlier Landry[2] had described cases of ascending paralysis which some authorities regard as part of this syndrome.

After an extensive survey of the literature, Haymaker and Kernohan,[3] in their classic monograph concerning this disease, reached the following conclusions:

"1) that the term Landry's paralysis has, through common usage, been confined to only one of the three forms Landry described, namely a strictly motor disorder which begins in the lower limbs and advances steadily upwards, 2) that a comparable descending form, starting in realm of the cranial nerves, occurs, 3) that the Guillain-Barré syndrome, as originally described, is a disorder in which motor involvement is striking, but in which the degree of sensory involvement varies considerably but is not total, the syndrome constituting a certain narrow group within the broad confines of the malady by virtue of the restrictions placed by Guillain and Barré on the amount of protein and the number of cells in the spinal fluid, 4) that a form characterized by an equal involvement of motility and sensibility exists, and 5) that many forms, the majority in fact, bridge the gaps between the four mentioned. The literature strongly indicates that from the clinical standpoint all forms are initially polyradiculoneuritis. There are indications that the morbid process may also involve the neuraxis."

Little concerted attention was devoted to neuronitis in children prior to the work of Debré and Thieffry,[4] who studied 32 cases and pointed out that it undoubtedly occurs more frequently than had hitherto been suspected. From a study of 5 cases of her own, as well as 94 collected from world literature, Aylett[5] concluded that infectious neuronitis assumes essentially the same form in children and adults and that the mortality rate generally is low. She made this statement in spite of the fact that 7 of the 99 patients in her series had died. This paucity of reports encouraged us to re-examine our experience with this illness in children.

MATERIAL STUDIED

We reviewed the records of all children, 15 years of age or less, seen at the Mayo Clinic from the years 1945 through 1957 who were given a diagnosis of neuronitis. Twenty-six cases were felt to meet the criteria for the diagnosis of this disease.

CLINICAL OBSERVATIONS

In reporting our clinical observations we shall make reference also to pertinent observations reported in the literature.

Age and sex. Our patients ranged in age from 16 months to 15 years. Three were less than 2 years of age, 6 were 2 through 4 years, 9 were 5 through 7 years, 1 was in the 8- through 10-year group, 5 were 11 through 13 years of age, and 2 were between the ages of 14 and 15.

Aylett[5] noted a similar distribution in the 61 patients on whom data existed concerning their

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age; namely, that the disease began before 8 years of age in approximately two-thirds of the cases. Debré and Thieffry[4] gave no specific information concerning ages of their patients but remarked that the majority were between 2½ and 4 years. The youngest patient whose case has been reported was 15 months.[6]

Our series consisted of 19 males and 7 females. The cause for the preponderance of males is not evident. In other series males and females have been equally affected.

Antecedent infections. Many authors have speculated on the significance of infections preceding the onset of neuronitis. Of our patients, 18 had suffered from antecedent infections; 11 had had upper respiratory infections. In 1 of these 11 patients, a single convulsion occurred during the respiratory infection. Two children had had otitis media. One child had had measles, and another had a rash of undetermined type. In 2 instances, indefinite symptoms of listlessness, anorexia, and low grade fever had antedated the onset of neuronitis. In 1 child, repeated infections were associated with agammaglobulinemia. Eight patients had given no history of prior infection.

Our figures are in accord with those of other writers who have emphasized that some type of infectious process often precedes the development of neuronitis.

In our patients, the interval between the infectious disease and onset of neuronitis varied from three months to two weeks. The rather long interval in some instances raises the possibility that the antecedent illness was coincidental.

Motor involvement. In all cases, the outstanding complaint was progressive muscular weakness. Weakness of legs signaled the onset in the vast majority of patients, and all patients had weakness of the lower extremities at some stage of the neuronitis. From the history, we usually could not differentiate weakness of proximal muscles from that of distal muscles, although the history of a waddling gait occasionally suggested initial involvement of muscles of the pelvic girdle. At the time we first examined our patients, which varied from two days to one year after the onset of neuronitis, the degree of weakness in proximal and distal muscles of the limbs was about equal in 16 cases; distal weakness predominated in 8 cases, and proximal weakness was more apparent in 2 cases. In all patients, the paresis was bilaterally symmetric. The upper extremities were involved less often and less severely. However, 6 children became quadriplegic before recovery. In all cases, paralysis was flaccid in type.

In spite of severe weakness or complete paralysis, the involved muscles did not atrophy often. In a 4-year-old girl, widespread atrophy was present on examination three months after the onset of neuronitis; however, she ultimately made a complete recovery. In another patient, a boy 15 years of age, atrophy of the muscles of the calf remained for one year after onset of the disease. At no time were fasciculations observed in any muscles. Some children gave a false impression of generalized muscle wasting which was, in fact, the result of atrophy of subcutaneous tissues attendant on general debility associated with the illness.

Impairment of bladder or bowel function developed in 2 patients. Flaccidity of the anal sphincter was observed in 1 child; another had urinary and fecal incontinence during his illness.

Involvement of cranial nerves. Muscles innervated by cranial nerves were affected in a total of 11 children. The seventh cranial nerve was affected in 6 patients, all of whom had bilateral facial weakness. Function of the eleventh cranial nerve was impaired bilaterally in 6 cases. In 2 patients, bilateral involvement of the eleventh cranial nerve was associated with bilateral seventh nerve paralysis. Dysphagia, implying involvement of the tenth cranial nerve, was reported in 4 instances; in 3 children, the dysphagia developed during hospitalization. Examination revealed unilateral paralysis of the tongue in 1 patient. In 6 children, more than 1 pair of cranial nerves was involved. Paralysis of the extraocular muscles was not observed, although 2 children complained of double vision.

Ophthalmoscopic examination revealed bilateral papilledema in 1 patient. Protein content of the cerebrospinal fluid in this 13-year-old boy was 800 mg. per 100 cc., the highest value recorded in our series. This is of interest because some authors[7] consider that papilledema results from an extreme elevation in the amount of protein in the cerebrospinal

fluid. A more recent opinion[8] is that the papilledema results from benign intracranial hypertension. In our patient, papilledema subsided with clinical recovery.

Sensory disturbances. Pain and paresthesia were complaints of 7 patients. Usually, children complained of pain in the legs and feet. In several cases, pain in the neck was mentioned. Paresthesia appeared early in the course of illness and was usually intermittent, affecting the lower extremities predominantly and tending to subside with the passage of time. Examination disclosed definite muscular tenderness in 7 patients. Eleven children had limitation of flexion of the neck.

Impairment in perception of vibration, often associated with a decrease in proprioceptive sensibility, was the outstanding objective sensory deficit. Such defects were found in 7 patients. One child was unable to perceive pinprick and light touch over the lower extremities. It should be borne in mind, however, that sensory examination in younger children is not precise, and our figures, therefore, may underestimate the frequency of sensory deficits.

Changes in reflexes. Guillain, Barré, and Strohl[1] regarded abolition of the tendon reflexes with conservation of cutaneous reflexes as a diagnostic criterion of the syndrome. At the time of examination, muscle stretch reflexes were diminished or absent in all except 1 of our patients. This patient had had normal stretch reflexes when examined during a remission. Areflexia developed in a subsequent relapse. Depression of muscle stretch reflexes tended to parallel the degree of muscular weakness, and reduction of these reflexes was usually greatest in the lower extremities. Although abdominal reflexes may be difficult to elicit in children, they were recorded as absent in 5 of our cases.

RESULTS OF LABORATORY EXAMINATIONS

Cerebrospinal fluid from 25 of the 26 patients was examined. In all but 1 patient, the fluid contained less than 6 cells per cubic millimeter. The spinal fluid obtained from this patient, who suffered from agammaglobulinemia, contained 28 lymphocytes per cubic millimeter. The child had had numerous preceding infections which may have produced pleocytosis.

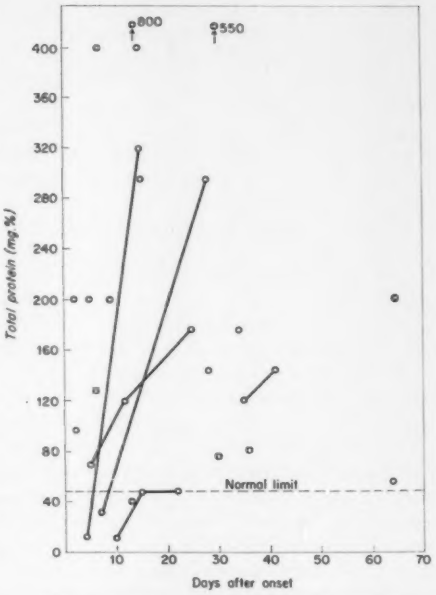

Fig. 1. Protein content of the cerebrospinal fluid at various intervals after onset of symptoms. Some determinations made more than seventy days after onset have been omitted from the illustration.

The protein content of cerebrospinal fluid exceeded 40 mg. per 100 cc. at some time during the illness in all patients. The highest value was 800 mg. A second examination of spinal fluid was made on only 8 patients. The relation of protein content to the time of onset of neuronitis is shown in Figure 1. The protein content may rise as soon as two days after onset of symptoms. In general, however, maximal elevation was encountered in ten to twenty-five days. In several instances, the elevation persisted as long as six months. These data seem in accord with those of Debré and Thieffry[4] and Kernohan and Haymaker.[3]

Electromyographic examinations were made in 10 cases by Dr. E. H. Lambert, Section of Physiology. These revealed, in all cases, features compatible with involvement of lower motor neurons or peripheral nerves.

In neuronitis, examination of the electric

activity of muscle with a needle electrode reveals [1] a reduction in number of motor-unit action potentials during a maximal voluntary contraction but maintenance of an essentially normal contour and size of the potentials and [2] the occurrence of fibrillation potentials in the resting muscle after the second or third week of illness. The reduction in motor-unit activity is in proportion to the degree of weakness of the muscles. However, the amount of fibrillation frequently is less than expected; this is in harmony with other evidence that often some axons fail to conduct impulses without undergoing wallerian degeneration. Other axons degenerate and leave denervated muscle fibers which produce fibrillation potentials.

Studies of conduction were carried out on the median, ulnar, and peroneal nerves. The muscular response to maximal stimulation of these nerves was reduced in magnitude. Often, the response of a muscle was greater when the nerve was stimulated near the muscle than when it was stimulated at a distance from the muscle. Velocity of conduction in the excitable motor fibers of the nerves was normal or slightly reduced in patients examined during the first few weeks of their illness but was definitely below the range of normal values in patients examined eight to fifty weeks after onset of the illness.

Five patients were examined within the first five weeks of their illness. Of these, 2 examined during the first week had conduction velocities at the lower limit of normal. In another, conduction velocity measured three days after onset of symptoms was normal, but examination on the eleventh and twenty-fifth day revealed that the nerves were unresponsive to stimulation. In 1 patient examined in the fourth week of illness, conduction velocity in the proximal part of the peroneal nerve (knee to ankle) was normal, but conduction in the distal part of the nerve was slow. The nerves of a patient examined in the fifth week of illness were not excitable. Seven patients were examined eight to fifty weeks after the onset of their illnesses. In 2, nerves remained unresponsive to stimulation twenty-three and thirty-three weeks after the appearance of symptoms; 5 had conduction velocities ranging from 10 to 42 (normal, 47 to 72) meters per second.

COURSE OF ILLNESS

Seventeen patients recovered from neuronitis and showed no residual neurologic deficits. Of these, 6 recovered completely within six months, 3 within six to twelve months, and 8 in one to three years. Two of these 17 patients had relapses. A 13-year-old boy recovered from the first episode in two months; however, five months later his weakness recurred and the second episode was more severe than the first. The other child also virtually recovered from an episode of neuronitis, although slight weakness of the hands remained. Nine months after the first symptoms had appeared, paresthesia and weakness returned. The second episode also was more severe than the first. Ultimately, both patients recovered completely.

Seven patients had persistent weakness and atrophy of muscles three to five years after the onset of neuronitis. In 6 of these, the weakness and atrophy involved muscles of the legs and feet. One child had weakness and atrophy of the intrinsic muscles of the hands.

One patient died during the acute phase of his illness. One was lost to follow-up study.

As mentioned before, 6 patients became quadriplegic during their illness. One of these died of pneumonia at the height of his illness, when he was suffering from weakness of the muscles of respiration. Two patients recovered completely in eight and eleven months respectively. The remaining 3 had protracted illnesses with persistent neurologic deficits.

ILLUSTRATIVE CASE

A 5-year-old girl was registered at the Mayo Clinic on September 26, 1956, because of muscular weakness. She had been in good health until four weeks prior to our examination, when her parents had noticed that she had difficulty in running and was unable to walk up stairs. During the next few days, weakness progressed and she began to lose strength in her hands. After hospitalization in her home community, the child was referred with a diagnosis of muscular dystrophy.

Physical examination revealed a pale, apathetic, cachetic girl who was 43 in. tall and weighed 36 lb. (Fig. 2). Abnormal findings were limited to the neurologic examination. All muscle stretch reflexes were absent. All the muscles of the arms and shoulder girdle were weak, but paresis was greatest in the distal muscles. A similar distribution of weakness was detected in the legs, and she was unable to hop, rise from a squatting posi-

tion, or stand on tiptoe. Her posture was lordotic. Because of weakness of proximal muscles of the hips, she walked with a waddling gait. Her muscles were flabby, but atrophy could not be detected.

Stimulation with a pin or the touch of a wisp of cotton was everywhere perceived normally. Although she invariably identified the vibration of a tuning fork on her fingers, she frequently failed to identify this stimulus at the ankles.

Estimation of the hemoglobin and number of leukocytes and erythrocytes gave normal values. Urinalysis disclosed no abnormal findings. Lumbar puncture thirty-three days after onset of symptoms revealed clear, colorless fluid under normal pressure. The fluid contained 2 lymphocytes per cubic millimeter and 180 mg. of protein per 100 cc. Electromyography revealed normal motor-unit action potentials. No fibrillation or fasciculation potentials were seen. Electric stimulation of the peroneal nerve disclosed prolongation of conduction time from ankle to foot (5.5 milliseconds, normal 2.5 to 3.5 milliseconds) as well as increased duration of the action potentials of the extensor digitorum brevis muscle to 12.5 milliseconds (normal 4.2 to 6.4 milliseconds).

A diagnosis of infectious neuronitis was made, and the parents were advised to keep the child at rest. They were instructed in a program of mild exercises to maintain normal joint motion.

The child was reexamined in January 1957. She had become progressively weaker until, by mid-December 1956, she had been unable to feed herself, sit, stand, walk, or turn over in bed. However, after mid-December she began to improve, and her strength increased. At reexamination, she could walk across the room though her gait was somewhat unsteady. She had a good grip in both hands. There was only mild weakness in the lower limbs. A program of muscle strengthening exercises was begun. She was last examined in April 1957, when her parents regarded her as completely recovered. She appeared healthy and robust (Fig. 3). No weakness could be detected and her muscles were of normal size. Muscle stretch reflexes had returned to normal. All modalities of sensation appeared normal.

This patient's illness typifies neuronitis. Weakness began insidiously and progressed for four months to quadriplegia. The paretic muscles were flaccid but without atrophy. Muscle stretch reflexes, which were absent, returned pari passu with clinical recovery that consumed another four months. Sensory defects were minimal. Three weeks after onset of the illness, the concentration of protein in the spinal fluid was elevated but pleocytosis did not appear. Electromyography revealed normal motor-unit potentials (in contrast to the findings in muscular dystrophy) but slowing of conduction in the peripheral nerves.

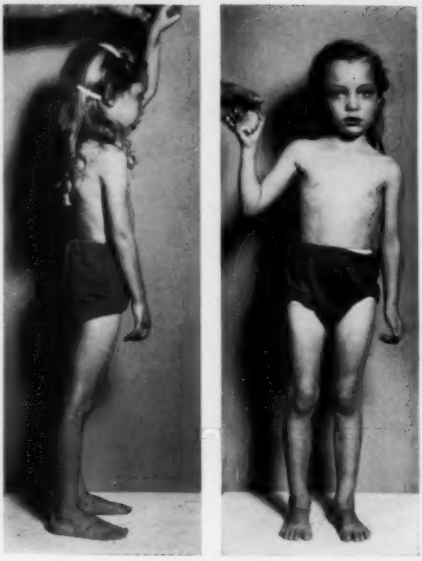

Fig. 2. Appearance at the height of illness. Patient was emaciated and unable to walk alone.

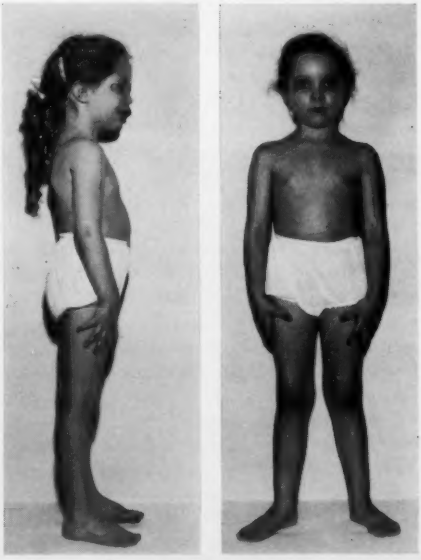

Fig. 3. Appearance six months later. Recovery is complete.

DIAGNOSIS

Infectious neuronitis is characterized by a gradual onset with progression of weakness over several weeks. Manifestations of systemic illness, such as fever and leukocytosis, are lacking, although the patient may appear wan and listless even early in the course of the disease. In our cases, involvement of the motor nerves predominated over that of the sensory nerves, muscular weakness being symmetric. The degree of areflexia paralleled the weakness. In children, sensory involvement is not prominent and, when present, usually consists of defects in proprioception and appreciation of vibration.

If the typical constellation of signs and symptoms is evident in a given case, diagnosis should not be difficult. However, the course and extent of neuronitis vary widely in different patients. When the disease is incompletely developed, problems in differential diagnosis may arise. Acute anterior poliomyelitis is characterized by a more rapid onset, and the muscular weakness, which is asymmetric, appears during the febrile stage and may be followed by muscular atrophy. No sensory defects occur. Characteristic laboratory findings include pleocytosis in the cerebrospinal fluid and essentially normal conduction velocity of peripheral nerves on electromyographic examination.

The diagnosis of muscular dystrophy was considered seriously in a number of our cases. This disease has a far more chronic course than neuronitis and may extend over many years. No remissions occur. In specific subcategories of muscular dystrophy, selective muscular weakness appears. In contrast to neuronitis, weakness parallels the degree of muscular atrophy. In many instances of muscular dystrophy, other members of the family may have had similar trouble. Sensory perception is unimpaired in muscular dystrophy, and cerebrospinal fluid is normal. Electromyographic study shows motor-unit action potentials of short duration and low amplitude. These are numerous in proportion to the strength of contractions. Conduction velocities of peripheral nerves are normal.

Polymyositis is a rare disorder which may be confused with neuronitis in its acute stage. In polymyositis, the patient appears systemically ill with fever, malaise, and often with cutaneous eruptions. Initially, muscle involvement is widespread, but frank paralysis is rare. No sensory defects develop. Laboratory studies reveal leukocytosis and increased sedimentation rate of erythrocytes; the cerebrospinal fluid is normal. Electromyography discloses primarily a decrease in size, rather than number, of motor-unit action potentials. Conduction velocities of peripheral nerves are normal.

Various writers[9] have commented on the association of certain systemic diseases with neuronitis. The nature of this association is not clear since no one systemic disease is constantly associated with neuronitis, and, conversely, in most cases neuronitis develops without evidence of systemic disease. The illnesses most commonly mentioned in association are infectious mononucleosis, infectious hepatitis, and diabetes mellitus. No children in our series gave evidence of such diseases.

TREATMENT

Since infectious neuronitis is not a specific entity, management involves general supportive measures such as limitation of activities or rest in bed, together with passive physical therapy to involved muscles during the acute stages. Bulbar or respiratory muscle weakness demands appropriate care. We have not used cortisone therapy, although some rather dramatic responses to administration of cortisone have been claimed.[10] In our experience, patients tend to recover without specific therapy. In the minority of patients with residual muscular weakness, rehabilitative physical therapy will be necessary.

COMMENT

Most children recover, although the illness may last two or three years and relapses can occur. Residual neurologic defects occur most frequently in severely affected patients, especially those with quadriplegia. The mortality rate of neuronitis in children is considerably less than that reported in adults. Various writers[3] have observed mortality rates in adults ranging from 20 to 67%.

SUMMARY

Data have been reported concerning clinical observations, laboratory examinations, and course of illness in 26 cases of infectious neu-

ronitis developing in children less than 16 years of age. In approximately two-thirds of the cases, the disease occurred before the age of 8 years, although ages ranged from 16 months through 15 years. The ratio of males to females was greater than 2.7 to 1. Antecedent infection had occurred in 18 patients, although in some this may have been coincidental.

Progressive symmetric muscular weakness was the chief complaint. Involvement of muscles of the limbs occured most often; however, in almost half the patients, weakness developed in muscles supplied by cranial nerves. Areflexia was present in all patients at some time in the illness.

Although sensory disturbances were not common, impairment in perception of vibration and proprioception was found in 7 patients.

Examination of the cerebrospinal fluid in 25 cases revealed albuminocytologic dissociation in all but 1 case, the protein attaining its highest level ten to twenty-five days after appearance of clinical symptoms. Electromyographic examinations revealed features compatible with involvement of lower motor neurons or peripheral nerves in the 10 patients so examined. Reduction in conduction velocity of peripheral nerves was a frequent observation, particularly after the first month of illness.

The course of the disease was prolonged in 11 of the 17 patients who, nevertheless, recovered completely from six months to three years later. Two of these patients had relapses. Seven had persistent weakness and atrophy of distal muscles of the legs three to five years after onset of their disease. One died of pneumonia secondary to weakness of the muscles of respiration. One was lost to follow-up study.

Problems in differential diagnosis are important as neuronitis may be confused with poliomyelitis, muscular dystrophy, or polymyositis.

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Glutamic oxalacetic transaminase (GOT) and lactic dehydrogenase (LDH) activities

Study in the cerebrospinal fluid of brain tumor patients, in normal human brain, and in brain tumor homogenates

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THE CEREBROSPINAL FLUID glutamic oxalacetic transaminase (GOT) and lactic dehydrogenase (LDH) activities are frequently increased in vascular, demyelinating, and neoplastic diseases of the nervous system.[1–3] We reported that LDH activity in the cerebrospinal fluid of brain tumor patients was consistently elevated.[2] The GOT activity was increased less frequently and to a lesser degree. Additional patients have since been studied and will be the subject of this report.

The possibility existed that the difference between the LDH and GOT activities in the cerebrospinal fluid of brain tumor patients reflected the content of the tumors themselves. We therefore decided to determine the LDH and GOT activities of frequently encountered brain tumors. These values were also determined for a normal human brain as a basis for comparison.

The soluble proteins of some brain tumors were studied by paper electrophoresis, and preliminary results will be reported.

MATERIALS AND METHODS

Cerebrospinal fluid was obtained by lumbar puncture from 16 patients who were later found to have intracranial tumors at operation or autopsy. Because fluid collected during air studies was found to contain unpredictably elevated enzyme activities,[2] it could not be used in this study. None of the fluids had an elevated red or white blood cell count.

Cerebrospinal fluid GOT and LDH activities were each determined by spectrophotometric methods, at 37° C. The principles and precautions necessary in these assays have been described elsewhere.[1,2] Values were expressed in μM. of product formed per hour per 100 cc. of cerebrospinal fluid.

Normal cerebrospinal-fluid GOT activity, as previously reported,[1] was 43 ± 12 μM. of oxalacetate formed per hour per 100 cc. at 37° C., ranging from 25 to 62. Normal cerebrospinal fluid LDH activity, as previously reported,[2] was 68 ± 15 μM. of lactate formed per hour per 100 cc. at 37° C., ranging from 31 to 87.

PREPARATION OF BRAIN HOMOGENATE

An intact human brain was obtained at autopsy of a 16-year-old girl who died of rheumatic heart disease. She had no neurologic symptoms or signs before death, and the brain was grossly and microscopically normal. The leptomeninges were stripped, and sections were taken from each lobe of the cerebrum and from the cerebellum. The cortex in these areas was separated from the subcortical white matter. Each specimen was homogenized in a Ten Broeck glass homogenizer with 5 times the tissue weight of isotonic saline. The whole homogenate was spun at 12,000 rpm in a Serval centrifuge for fifteen minutes at 4° C. The resultant clear supernatant was diluted and assayed for GOT and LDH activities. In addition, the protein content of each supernatant

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TABLE 1

CEREBROSPINAL FLUID LDH AND GOT ACTIVITIES OF 16 PATIENTS WITH MICROSCOPICALLY VERIFIED BRAIN TUMORS

Tumor	*GOT*	*LDH**
	μM per hour per 100 cc.	
Meningioma	62	164
	71	102
	90	115
	87	112
Pituitary adenoma	62	102
Astrocytoma	80	155
	37	127
	56	164
	60	124
Glioblastoma	53	124
	83	350
	68	248
	80	149
Metastatic carcinoma		
1° lung	71	428
1° lung	124	360
1° breast	84	115

*at 37° C.

was determined by both turbidimetric and biuret methods. The homogenization and analyses described above were completed within ten hours after death.

PREPARATION OF BRAIN TUMOR HOMOGENATES

At operation, 5 tumors were obtained. Sections of these tumors were selected for study which were free of hemorrhage and contained no grossly apparent brain tissue. No attempt was made to examine different zones of these neoplasms. The tissue was homogenized with isotonic saline in a fashion similar to that described above for normal brain. Suitable dilutions of the supernatant were chosen for GOT and LDH analyses, and the protein content of each was determined by turbidimetric and biuret methods. Each tumor was studied within four hours of removal. Specimens were refrigerated, but not frozen, until the analyses could be performed. Examination was made for enzymatic activity and protein content of 2 specimens of cyst fluid removed from astrocytomas during operation. Electrophoretic separations of tumor homogenates and cyst fluid were accomplished in a Durrum type hanging strip cell (manufactured by Spinco) using Veronal buffer, *p*H 8.6, ionic strength, μ 0.05, on Whatman 3 MM paper. A current of 6 ma was maintained for sixteen hours. The strips were then dried and denatured and stained with bromophenol blue and Sudan IV. Quantitation was done with a Spinco Analytol.

RESULTS

Table 1 presents the cerebrospinal-fluid enzyme activities in 16 patients with brain tumor. The tumors are grouped according to histologic diagnosis. LDH was increased in all patients. With a few exceptions, the greatest activities were associated with metastatic carcinomas to the brain and glioblastomas, the least with meningiomas and pituitary adenoma. The cerebrospinal-fluid LDH activity of the patients with astrocytomas fell between these 2 groups.

GOT elevations were less frequent, occurring in 9 of the 16 patients. Except for a value of 124 μM., observed in 1 patient with metastatic carcinoma, the GOT activities with benign and malignant lesions were of a similar order.

Table 2 lists the enzyme activities determined in the anatomical divisions of the normal brain according to fresh wet weight and to the protein content of the supernatant homogenate. The greatest concentrations of both GOT and LDH were present in the gray matter of the cerebrum and cerebellum, the lowest in the corpus callosum and parietal white matter (corona radiata). The GOT results are in good agreement with the data reported by Braunstein[4] and by Wakin and Fleisher.[5] These latter workers found the GOT concentrations of the cerebral and cerebellar cortices of dogs to be 390 and 550 μM. per hour per gram of fresh weight, respectively. Transamination in

TABLE 2

LDH AND GOT ACTIVITIES OF A NORMAL HUMAN BRAIN BASED ON FRESH WEIGHT AND SOLUBLE PROTEIN

Section of brain	*GOT*	*LDH*	*GOT*	*LDH*
	*μM per gram of fresh weight per hour**		*μM per gram of protein per hour**	
Frontal (gray)	1,220	5,000	347,000	1,388,000
Parietal (gray)	679	4,100	231,000	1,366,000
Parietal (white)	446	3,300		
Temporal (gray)	353	5,300	98,000	1,476,000
Occipital (gray)	538	5,600	148,000	1,456,000
Cerebellum (gray)	595	6,700	168,000	1,850,000
Corpus callosum	298	3,600	91,800	1,102,000

*at 37° C.

TABLE 3

LDH AND GOT ACTIVITIES OF BRAIN TUMORS AND CYST FLUID BASED ON FRESH WEIGHT AND SOLUBLE PROTEIN

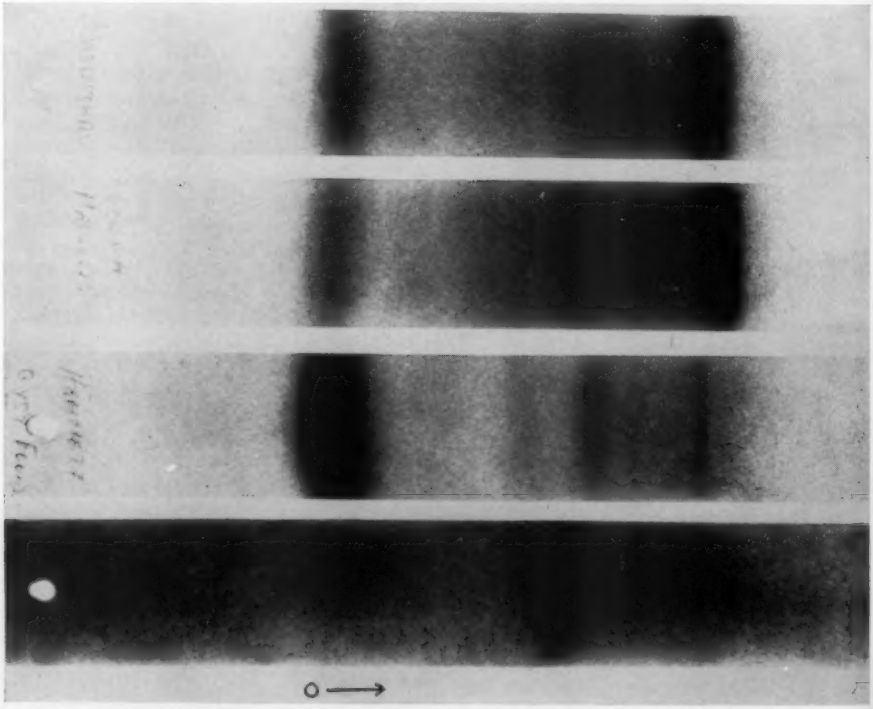
Tumor	GOT μM per gram of fresh weight per hour*	LDH	GOT μM per gram protein per hour*	LDH
Glioblastoma	603	7,870	20,150	282,880
Glioblastoma	672	11,840	20,031	353,000
Glioblastoma	990	8,200	6,930	69,000
Meningioma	1,716	26,730	16,120	251,100
Meningioma	534	7,750	21,100	306,100
Astrocytoma (cyst fluid)	682	6,510	111	1,067
Astrocytoma (cyst fluid)	713	16,306		

*at 37° C.

the brains of dog and man is thus very similar.

Table 3 lists the GOT and LDH activities of 5 brain tumors and 2 samples of cyst fluid from astrocytomas. The activities are referred to both fresh weight and the soluble protein. No correlation existed between either the GOT or LDH content of a neoplasm and its histologic type. A meningioma had a higher concentration of these enzymes than did the malignant gliomas and metastatic carcinomas.

A comparison of Tables 2 and 3 reveals that, based on fresh weight, the group of neoplasms contained greater GOT and LDH activities than did the normal brain. They possesed considerably less activity, however, per gram of soluble protein. Expressed another way, the



Paper electrophoretic separations of brain tumor homogenates and cyst fluid. Upper strip: glioblastoma. Immediately below: meningioma. Lower 2 strips: astrocytoma cyst fluid. All strips were stained with bromophenol blue except for the second sample of the astrocytoma cyst fluid (lowest strip) which was stained with Sudan IV. O = origin.

neoplasms contained approximately 10 times more soluble protein than the brain tissue. Of the astrocytoma cysts fluids, No. 6 had a protein content of 6 gm. per 100 cc.—similar to serum in this respect—but had considerably more enzymatic activity than serum. Mean serum LDH and GOT, as determined in this laboratory, are 1,240 and 93 μM. per hour per 100 cc. at 37° C.

The electrophoretic separations are pictured in the illustration. The strips of both the glioblastoma and meningioma had dense bands at the point of application which probably represent denatured protein and cellular debris. Both strips had good albumin bands. No prealbumin fraction could be detected. Only a trace of gamma globulin was apparent in either strip. Alpha$_1$-, alpha$_2$-, and beta-globulin fractions were discernible in both strips, but, in addition, the meningioma had a definite band in the theta region. The Sudan preparations of the tumor extracts were unsuccessful.

The separation of the cyst fluid resembled serum separations with the exceptions of a better resolution of the albumin and alpha$_1$-globulin fractions and the presence of a faint beta$_2$-globulin fraction. Sudan black treatment revealed a densly staining fraction which migrated with the alpha$_2$-globulin.

DISCUSSION

The enzymatic activity of normal brain tissue is difficult to compare with that of brain tumors. No truly comparable basis exists for the expression of specific activity. When activity was related to fresh weight, tumors had more LDH and GOT than normal brain tissue. Much of the fresh weight of the brain is due to its high fat content.[6] If an approximate correction was made for this by choosing the soluble protein content as the basis for activity, the brain tissue had greater concentrations of LDH and GOT than did any tumor. This was true also because the tumor homogenates contained a large amount of soluble protein. Therefore, the difference between brain and tumor tissues in respect to LDH and GOT activities was as much indicative of a dissimilar fat and protein content as of different enzyme concentrations.

Although the brain tumors possessed considerable GOT and LDH activity, only the LDH was consistently increased in the cerebrospinal fluid of the patients. In general, this increase was greatest in patients with malignant lesions, which themselves did not differ significantly from benign tumors in their LDH concentration. These results are in agreement with those obtained by Analyan and Starr who determined beta-glucuronidase activity in cerebrospinal fluid and brain tumors.[7] They found that malignant gliomas were often associated with elevations of this enzyme in the cerebrospinal fluid. However, the beta-glucuronidase content of benign and malignant tumors was similar.

The source of the additional enzymes in the cerebrospinal fluid of tumor patients was not identified by this study. Necrosis of a tumor or the brain adjacent to the tumor should release GOT, as well as LDH, into the cerebrospinal fluid. This would be expected because of the considerable GOT activity present in both brain and tumor homogenates. Perhaps there is a selective release of enzymes from viable neoplastic cells rather than an extrusion of all the intracellular enzymes—as would occur in necrosis.

Animal experiments have shown that neoplastic cells are capable of releasing LDH at a rapid rate.[8] We observed marked increases in the cerebrospinal fluid enzyme activities of patients undergoing pneumoencephalography.[2] This may indicate that, under certain conditions, cells can release enzymes while retaining viability.

Brain tumors may alter the permeability of the blood-brain barrier, thus allowing serum enzymes to enter the cerebrospinal fluid. If so, the LDH level of the cerebrospinal fluid would be increased more proportionately than the GOT because the LDH serum per LDH cerebrospinal fluid is 1240/68, while the GOT serum per GOT cerebrospinal fluid is 93/43 (figures in μM.). This mechanism could produce the disparity between GOT and LDH activities in the cerebrospinal fluid of patients with brain tumors.

In this discussion, enzyme activity has been tacitly equated to the actual enzyme concentration. Increases in enzyme activity in cerebrospinal fluid may result from the addition of activators or the removal of inhibitors. A search for these factors has so far failed.[9]

An attempt was made to characterize the soluble protein of the tumor homogenates by paper electrophoresis. A meningioma and glioblastoma were found to differ in certain fractions. More tumors are being studied to see if this difference is consistent. The electrophoretic pattern of the astrocytoma cyst fluid was almost identical with that of a sample of similar total protein content pictured by Cumings.[10]

SUMMARY

The LDH activity was increased in the cerebrospinal fluid of all 16 brain tumor patients studied. The highest levels were present in patients with malignant tumors. GOT activity was increased in 9 patients. Homogenates of benign or malignant tumors had more GOT and LDH activities than normal human brain tissue preparations on a fresh weight basis but much less per gram of protein. Tumors contained considerably more soluble protein than brain tissue.

The elevations of cerebrospinal fluid enzyme activities which occurred in the patients with brain tumors are not fully explained by the enzyme concentrations of the tumors. The origin of the additional cerebrospinal fluid enzyme remains uncertain.

Preliminary electrophoretic studies were carried out on tumor homogenates and cyst fluid.

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Evaluation of phosphohexose isomerase activity in cerebrospinal fluid in neoplastic disease of the central nervous system

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ONE OF THE RECENT developments of interest in clinical biochemistry is the application to diagnostic and pathophysiologic problems of enzyme assays in body fluids. The striking elevation in serum glutamic-oxalacetic transaminase activity following myocardial infarction[1] has been of clinical usefulness. Significant changes in serum enzyme levels have been documented in other disease states, including neoplastic disease, pathologic conditions of the liver, myopathies, muscular dystrophies, and some degenerative diseases of the nervous system.[2]

In general, these pathologic conditions do not cause elevated enzyme activity in the cerebrospinal fluid. Conversely, degenerative or neoplastic involvement of the central nervous system is usually not mirrored by changes in serum enzyme levels. In experiments with dogs, Wakim and Fleisher[3,4] found that high serum levels of glutamic-oxalacetic transaminase activity following experimental liver infarctions were not associated with comparable rises in spinal fluid activity. Intravenous injection of glutamic-oxalacetic transaminase concentrates produced rises in serum level but caused only transient, small elevations in spinal fluid activity. These findings were confirmed by Dunn and associates.[5] The Mayo Clinic group also found that intracisternal injections of the enzyme concentrate produced no significant increase in the serum activity.

A number of investigators interested in diseases of the central nervous system have looked for alterations in enzyme levels in the cerebrospinal fluid.[6–31] Most of these studies have been concerned with glutamic-oxalacetic transaminase and lactic dehydrogenase. The results of this search have varied. Generally, elevations have been reported for both these enzymes in patients with cerebrovascular accidents and infarctions. In patients with brain tumor, normal levels of glutamic-oxalacetic transaminase have been found repeatedly. Increases in lactic dehydrogenase have been demonstrated in some studies but not in others.

Bodansky[32] evaluated the changes of serum phosphohexose isomerase activity in the exacerbations and remissions of disseminated mammary and prostatic carcinoma under treatment; he observed that many tissues were rich in this enzyme. Assays of tissue homogenates indicated that the level of phosphohexose isomerase activity in brain was approximately 500 times greater than that of serum.

Bruns, Jacob, and Weverinck[33] had reported that phosphohexose isomerase activity is present in cerebrospinal fluid. On the basis of these findings, the activity of this enzyme was measured in samples of cerebrospinal fluid in a variety of patients with neoplastic disease and also in suitable control specimens.

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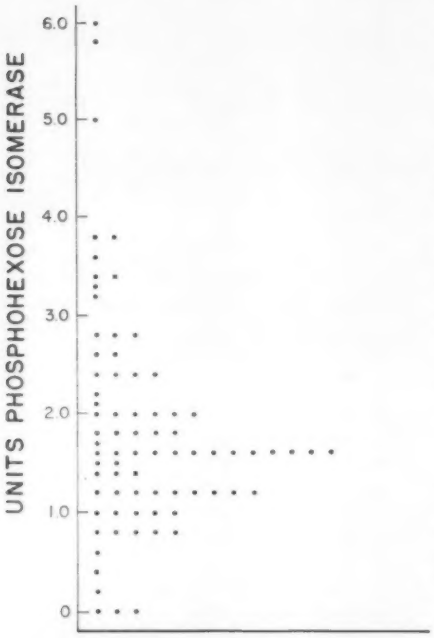

Phosphohexose isomerase values in cerebrospinal fluid of 76 control patients. Each of the dots represents 1 sample.

METHODS AND MATERIALS

The series to be reported consists of 133 specimens from an equal number of patients. Results on duplicate samples obtained on a few patients agreed consistently. Most of the samples of cerebrospinal fluid were entirely clear and colorless; the occasional turbid specimens were centrifuged promptly at about 2,500 r.p.m. for ten minutes at room temperature. Leukocyte and erythrocyte enumerations were carried out on almost all samples. The cell counts bore no relationship to the enzyme levels in the fluids, and contamination with blood cells cannot be considered a significant factor in the elevation of enzyme activity. Xanthochromic or bloody samples were discarded. Material obtained from pneumoencephalography is not included. The injection of air in the subarachnoid space created variable levels of phosphohexose isomerase activity which were frequently elevated and without apparent relationship to the presence or severity of the underlying disease process. This finding coincides with the experience of Green and associates[14] with another enzyme.

Phosphohexose isomerase was assayed by the method of Bodansky[32] based on the colorimetric determination of fructose-6-phosphate formed under standard conditions. The procedure outlined by this author for serum was found suitable for cerebrospinal fluid and was followed in all details except for the fact that the sample was not diluted prior to incubation with the substrate-buffer mixture. The units of enzyme activity were defined as the reciprocal of that concentration of cerebrospinal fluid, expressed as cubic centimeter per cubic centimeter of reaction mixture, that would cause the formation of 25 μg. of fructose under these standard conditions.

For comparative purposes, lactic dehydrogenase and glutamic-oxalacetic transaminase activities were also determined in a small number of cerebrospinal fluid samples. Lactic dehydrogenase was assayed by the spectrophotometric method of Hill and Levi[34] based on the disappearance of reduced diphosphopyridine nucleotide during incubation with pyruvate. For glutamic-oxalacetic transaminase, the method of Karmen,[35] as detailed by Steinberg and associates,[36] was employed. In this procedure, the transamination of α—ketoglutarate and aspartate to yield glutamate and oxalacetate is coupled to the reduction of oxalacetate to malate by reduced diphosphopyridine nucleotide in the presence of excess purified malic dehydrogenase. In both these procedures, 1 unit of enzyme activity was defined as a change in optical density of 0.001 per cubic centimeter sample per minute at 25° C.

The 3 enzymes were also assayed in a series of specimens of normal brain tissue and glioblastoma multiforme obtained at the time of craniotomy. In these experiments, tissue homogenates were prepared in distilled water in a Potter-Elvehjem all-glass homogenizer—usually within an hour after removal of normal brain or brain tumor. Suitable dilutions of these homogenates were assayed by the same procedures used for serum or cerebrospinal fluid. The units of enzyme activity in each instance were calculated on the basis of grams

wet weight, milligram total nitrogen, and number of cells (nuclei) per sample.

RESULTS

The illustration shows the distribution of the phosphohexose isomerase activity in the control cases. The material includes a variety of nonneoplastic diseases. The cerebrospinal fluid specimens in this series came from patients with multiple sclerosis, seizure disorders of unknown etiology, schizophrenic reactions, functional headache or back pain, hysterical reactions, parkinsonism, amyotrophic lateral sclerosis, myasthenia gravis, and cervical osteoarthritis.

The mean phosphohexose isomerase value in the control series of 76 specimens was found to be 1.85 units ± standard deviation (S.D.) 1.15 u. Since the distribution of values follows a normal probability curve, ± 2 S.D. was considered to define the limits of the control values. The range, which includes 96% of the observations, is from 0 to 4.2 u. Values close to this mean and well within the normal range were also found in a small series of samples obtained during spinal anesthesia from patients who had no central nervous system involvement.

Note in the illustration that 3 values are above the upper limits of this normal range. These 3 cases are suspect. K.R. (PHI 5.8 u.) was a patient with congenital hydrocephalus. He had had a ventriculopleural shunt in place for some months. He was not doing well, and, at the time the specimen was collected, the patient was having a revision of his tube. This result is included because the patient had no evidence of tumor or infection at the time the specimen was obtained.

L.C. (PHI 5.0 u.) was a patient with a clinical diagnosis of carcinoma of the head of the pancreas. At the time the cerebrospinal fluid specimen was obtained, she was jaundiced and in obvious hepatic decompensation. She did not, however, have any conclusive evidence of central nervous system metastasis, although metastasis may have been present. Permission for autopsy was not obtained.

J.G. (PHI 6.0 u.) was a patient done early in the series. The diagnosis at the time of discharge was "face pain of unknown etiology." The patient was lost to follow-up.

Tables 1 and 2 present the data on malignant and benign tumors of the nervous system. In both groups, all the known data are presented. In many of the samples, cerebrospinal fluid sugar was not determined. The cerebrospinal fluid was obtained from either the lumbar sac or ventricles.

Table 1 summarizes the results in 33 patients with malignant tumor of the brain, spinal cord, and cauda equina. As can be seen, a variety of primary and secondary neoplasms were studied. Of the 33 patients, 21 showed significant elevations in phosphohexose isomerase activity greater than the upper limit of the normal range; 12 had enzyme activities within the normal range, and, in 9 of the 12, the cerebrospinal fluid had been collected from the ventricle. Of 5 patients with glioblastoma, 4 had elevated enzyme activity. No obvious correlation existed between tumor type and enzyme activity.

Determinations of phosphohexose isomerase were carried out on samples of serum from a small number of these patients with brain tumors, including some of the patients with striking elevations of the enzyme levels in cerebrospinal fluid. As expected, all the serum values were within the normal range established by Bodansky[32] and confirmed in this laboratory in a series of control samples.

The benign tumors are presented in Table 2. The phosphohexose isomerase activity in this group was in the normal range (up to 4.2 u.) with 1 exception. This cerebrospinal fluid specimen was obtained during ventriculography and contained 770 red blood cells per cubic millimeter.

Table 3 presents the findings in 2 categories of neurologic disease which might be expected to be associated with phosphohexose isomerase elevations in the cerebrospinal fluid. These patients had central nervous system damage from cerebrovascular accidents (thromboses) and a variety of infections. Of 9 patients with cerebrovascular accidents, 2 had elevated enzyme activity. Of the 8 patients with infections, 4 had increase in phosphohexose isomerase activity.

The elevation in activity was not correlated with the presence of leukocytes or red blood cells and was also unrelated to increased protein or decreased sugar concentrations. The

TABLE 1
MALIGNANT TUMORS OF CENTRAL NERVOUS SYSTEM

	Name	Diagnosis	WBC	RBC	Protein	Sugar	PHI†
1.	B.S.	Astrocytoma of third ventricle	1		17*	90	0.3
2.	S.M.	Tumor of cerebellum (ependymoma?)	1	1,350	14*	94	0.5
3.	G.H.	Astrocytoma	1	251	13*		0.8
4.	L.S.	Glioblastoma	4		85		1.4
5.	M.W.	Metastatic carcinoma to cerebellum	1	5	<10*		1.6
6.	A.K.	Metastatic carcinoma to cerebellum	1	250	13*		1.8
7.	D.K.	Astrocytoma of left cerebellum			*		1.8
8.	S.B.	Astrocytoma of thalamus	1	193	10*		2.2
9.	E.O.	Carcinoma of lung metastatic to cerebrum	1		95	76	2.5
10.	A.M.	Melanoma metastatic to cerebellum	2	200	10*		2.9
11.	N.T.	Midbrain tumor	1	4	<10*	73	3.0
12.	R.T.	Carcinoma of larynx metastatic to right parietal lobe	3		52		4.2
13.	C.B.	Thalamic tumor	0		<10*	125	4.4
14.	D.D.	Ependymoma of fourth ventricle	1	320	13*		4.4
15.	F.P.	Carcinoma of cervix metastatic to central nervous system	21	670	40	86	4.6
16.	E.R.	Metastatic carcinoma to roof of fourth ventricle	1	30	31*	78	5.0
17.	M.L.	Carcinoma of breast, metastatic to skull	0		50	64	5.2
18.	A.M.	Plasmacytoma(?) of cauda equina	26	11	136		5.2
19.	C.F.	Hodgkin's disease with meningeal infiltration	13	11	41	44	5.2
20.	C.O.	Astrocytoma of brain stem, meningitis	102		113	47	5.4
21.	M.M.	Carcinoma of cervix metastatic to central nervous system	0	0	66	59	5.6
22.	A.K.	Carcinoma of lung metastatic to brain stem			67	57	5.8
23.	D.C.	Glioblastoma	1				5.8
24.	H.T.	Brain stem tumor		960	13*		6.2
25.	H.T.	Carcinoma of breast metastatic to brain stem	0	112	60		6.6
26.	S.H.	Medulloblastoma			28*		7.0
27.	H.K.	Pinealoma	150		184		9.6
28.	G.B.	Glioblastoma			90		10.4
29.	C.D.	Ependymoma	315	95	<10*		11.6
30.	F.S.	Glioblastoma	1	96	47		12.2
31.	A.L.	Glioblastoma	1	15	57		13.8
32.	F.M.	Carcinoma of lung metastatic to cerebellum	1	6,250			16.8
33.	R.S.	Brain stem tumor (during radiotherapy)	5		83		40.4

*Specimen obtained from ventricle
†Phosphohexose isomerase

TABLE 2
BENIGN TUMORS OF CENTRAL NERVOUS SYSTEM

	Name	Diagnosis	WBC	RBC	Protein	PHI†
1.	J.L.	Meningioma	1		65	0.4
2.	G.S.	Meningioma	1		202	1.4
3.	G.G.	Cerebellar hemangioblastoma	0	388	10*	1.4
4.	S.E.	Meningioma		1,830	100*	1.6
5.	A.F.	Myxoma of the meninges	1		49	2.4
6.	K.K.	Acoustic neuroma	1	13	127	3.0
7.	H.P.	Schwannoma of the eighth nerve		770	35*	5.8

*Specimen obtained from ventricle
†Phosphohexose isomerase

TABLE 3

	Name	Diagnosis	WBC	RBC	Protein	Sugar	PHI†
		INFARCTIONS					
1.	W.Z.	Cerebral embolism, hypertensive cardiovascular disease	1		48		0.6
2.	D.E.	1) cerebral thrombosis 2) hypertensive cardiovascular disease	1		49		1.8
3.	J.A.	1) cerebral thrombosis 2) non-specific vasculitis	1	100	38	67	2.0
4.	T.K.	Cerebral thrombosis	1	4	136		2.6
5.	R.D.	Cerebral thrombosis, diabetes mellitus	1		40		3.0
6.	S.M.	Platybasia with old posterior fossa adhesions and postoperative hemorrhage	1	800	23*		3.8
7.	M.S.	Basilar artery thrombosis					4.2
8.	A.R.	Cerebral thrombosis	4	400	100		5.2
9.	W.R.	Carcinoma breast and cerebral thrombosis					9.6
		INFECTIONS					
1.	C.L.	Bullet in brain, old abscess	18		49	74	1.4
2.	A.R.	T.B. meningitis (during treatment)	8	35	35		1.6
3.	I.L.	Encephalomyelitis	47	0	32	61	2.2
4.	A.P.	Encephalomyelitis	8		62		3.0
5.	H.M.	Meningoencephalitis	6	0	104		5.5
6.	L.S.	1) meningitis 2) chromophobe adenoma, post treatment	157	64	100	55	6.0
7.	S.A.	Acute poliomyelitis	9		62	88	7.2
8.	A.P.	Cryptococcal meningitis	10 (134 yeast cells)	2	197	26	8.6

*Specimen obtained from ventricle
†Phosphohexose isomerase

enzyme activity varied with the clinical severity of the infectious process and was elevated in the acute infections, but within normal range in chronic or subacute infections. No correlation was noted between the type of infection and the enzyme activity. In 1 patient with cryptococcal meningitis in whom many yeast cells were noted in the India-ink preparation, a suspension of yeast cells was made from the culture; phosphohexose isomerase activity was measured in this suspension and found to be present in amounts too small to account for the level measured in the patient's cerebrospinal fluid.

The activities of glutamic-oxalacetic transaminase and lactic dehydrogenase were determined in a small number of samples of cerebrospinal fluid from patients with nonneoplastic conditions and with brain tumors. Most of the values in both of these groups were within normal range. In addition, all 3 enzymes were measured in tissue specimens from a series of patients who had resections of brain tumors in which a small amount of normal brain was removed. Table 4 summarizes this data, using wet weight of tissue as the basis for calculation. The results show that there was no significant difference in enzyme activity between normal brain and brain tumors. The same general agreement was seen when the enzyme activities were expressed on a total nitrogen or cell basis. The last column of Table 4 relates the data obtained in cerebrospinal fluid to the amount of enzyme activity present in the tissues. It is of interest that the ratio of tissue enzyme activity/spinal fluid activity for phosphohexose isomerase was 3 to 7 times as large as for the other enzymes.

DISCUSSION

A number of chemical constituents of cerebrospinal fluid are under investigation as potential guides in the diagnosis and evaluation of the clinical course of various diseases of the central nervous system. The rapidly expanding literature on this subject indicates that altera-

TABLE 4
RELATION OF HUMAN BRAIN TISSUE LEVELS OF 3 ENZYMES TO CEREBROSPINAL FLUID LEVELS

	Normal brain	*Brain tumors*	*Non-tumor cerebrospinal fluid*	*Approximate tissue/cerebrospinal fluid ratio*
Phosphohexose isomerase				
Number of samples	7	15	76	
Average	27,000	24,000	1.85	14,000
Range	14,000–44,000	8,000–91,000	0–6.0	
Lactic dehydrogenase				
Number of samples	6	13	15	
Average	54,000	65,000	16	4,000
Range	26,000–81,000	15,000–210,000	5–33	
Glutamic-oxalacetic transaminase				
Number of samples	4	8	6	
Average	55,000	27,000	12	2,000
Range	42,000–73,000	8,000–53,000	6–20	

tions in the levels of protein, sugar, and several enzymes occur in a certain number of cases, but not with sufficient regularity to permit unquestioning reliance on these diagnostic aids.

The present data indicate that elevations in the phosphohexose isomerase activity of cerebrospinal fluid occurred in about two-thirds of the 33 patients with malignant tumors of the central nervous system included in this series. In these patients, the correlation with the presence of the disease was much greater for this enzyme than for lactic dehydrogenase and glutamic-oxalacetic transaminase, protein, or sugar. The greater sensitivity of changes in phosphohexose isomerase presumably may be related to the fact that its level in normal and neoplastic brain tissue in relation to its normal level in cerebrospinal fluid is considerably larger than that of the other 2 enzymes (Table 4).

In the entire series of 133 cases, the number of false positives—instances of elevated phosphohexose isomerase levels in cerebrospinal fluid in patients with central nervous system conditions other than malignant neoplasms—was small. It is of interest that only a few patients with cerebrovascular accidents had values above normal; of greater importance is the fact that 4 of 8 patients with infection had significant elevations.

A more cogent objection to the routine use of this diagnostic tool is indicated by the fairly sizable group of false negatives. At the present time, a definitive explanation cannot be advanced for the fact that normal enzyme levels were found in 12 of the 33 patients with malignant tumors of the central nervous system. The location of the tumor in relation to the site of collection of the sample of cerebrospinal fluid undoubtedly plays a major role. Ventricular fluid is likely to reflect the presence of only those neoplasms which are located near the ventricular wall; most of the normal values obtained in Table 1 were found in samples collected from the ventricles. A number of other factors may be involved—the extent of necrosis and tissue damage in and around the neoplasm, variable changes in membrane permeability, or the rate of progression of the disease process at the time the sample was obtained. Since alterations in the biochemical composition of body fluids as a consequence of various pathologic states can be interpreted in contradictory ways,[2] further work will be required to provide a rational explanation of these discrepant results.

Despite this limitation, however, the determination of phosphohexose isomerase activity in cerebrospinal fluid provides an additional diagnostic tool for the differential diagnosis of malignant neoplasms of the central nervous system. Review of the patients presented in Tables 1 and 2 shows that they all had the diagnosis established by conventional methods. The significance of the enzyme activity in any one instance would probably depend on the fact that a lumbar puncture with examination of the cerebrospinal fluid for phosphohexose isomerase activity represents a rather simple

and expeditious procedure which may suggest that malignant neoplastic disease is present. This information may be especially valuable in patients in whom the spinal fluid protein is within normal limits, as was the case in many of the patients with malignant tumors.

SUMMARY AND CONCLUSIONS

Phosphohexose isomerase activity has been measured in the cerebrospinal fluid in a control group of patients without demonstrable neoplastic disease and in patients with malignant and benign tumors, cerebral thromboses, and infections of the central nervous system.

The mean value of phosphohexose isomerase activity in the cerebrospinal fluid in the control series was 1.85 ± 1.15, with a range of 0 to 4.2 units.

Of 33 patients with primary or secondary tumors, 21 showed phosphohexose isomerase activity above the normal range. In these patients, no correlation was noted between the phosphohexose isomerase activity of cerebrospinal fluid and of serum.

No correlation was observed between phosphohexose isomerase activity and protein and sugar concentrations or white and red cell counts in the cerebrospinal fluid.

The phosphohexose isomerase activity was within normal limits in all but 1 patient with benign tumor.

Elevations were observed in half the patients with meningitis and meningoencephalitis caused by pyogenic, viral, or yeast organisms. The enzyme activity was elevated in the acute infections and normal in the chronic or subacute processes.

Phosphohexose isomerase activity was elevated in 2 of 9 patients with cerebral thrombosis.

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Blood viscosity in cerebrovascular disease

Effects of low fat diet and heparin

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THE RELATIONSHIP of the incidence of ischemia in vascular disease to the amount of the fat consumed is considered by many investigators to be due, in turn, to the development of atherosclerosis.[1–3] Recent observations of adhesiveness and aggregation of red blood cells, increase in the blood viscosity, and slowing of the circulation after large fat meals[4–9] suggest that, possibly, other mechanisms related to the blood itself may be of importance in the production of ischemia and infarction. These observations are particularly relevant in those cases in which occlusion of vessels cannot be demonstrated. Shortening of the coagulation time also has been thought to result from high fat meals.[10,11] Although the changes in coagulation time are controversial or slight,[12] they constitute an additional reason for considering the blood itself.

In the present paper, evidence is presented which indicates that there are changes (apparently not related to coagulation) in the blood viscosity and buffy coat of patients with cerebrovascular disease. These changes are less marked, less frequent, or not observed in people who are vigorous and in good health. Further, it will be shown that, when patients with relatively high blood viscosity follow a low fat diet during a period of six to thirty months, the viscosity approaches or reaches a relatively low level.

MATERIAL AND METHODS

Our low fat diet[13,14] contains 35 gm. of easily computed lipid. About 15 gm. is hard fat, the rest vegetable or fish oil. This diet has been in continuous use for ten and one-half years by many patients in the treatment of multiple sclerosis.*

Blood viscosity measurements in duplicate were determined on whole blood without anticoagulant using the method of Swank and Roth.[15] The blood viscosity is expressed in relationship to the viscosity of water under the same conditions of temperature and pressure. Usually it was 3.8 to 4.8 times the viscosity of water. Because the viscosity of whole blood is strongly affected by the hematocrit, a ratio of the blood viscosity to the hematocrit times 10 has come into use. This gives a figure referred to as the viscosity index.

$$\frac{\text{viscosity} \times 10}{\text{hematocrit}} = \text{viscosity index}$$

In all instances in which the viscosity index is used, the figure was derived from an average of at least 4 consecutive hematocrit and viscosity determinations. With a hematocrit below 50%, the viscosity index varies from about 0.85 to 1.20 and the relationship of the hematocrit to the viscosity is nearly linear. Whenever this ratio is 1 or less, we refer to the viscosity as being relatively low. Whenever the ratio is above 1, we refer to it as being relatively high. When the hematocrit exceeds 50%, the viscosity index normally increases and usually exceeds 1.† This is because the viscosity increases more rapidly than the hematocrit.[16].

RESULTS

Blood viscosity levels. The blood viscosity and hematocrit were determined repeatedly in

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*The low fat diet together with special recipes has recently been published in book form and is available through University of Oregon Books, Eugene. (Swank, R. L., and Grimsgaard, A.: Low Fat Diet. Reasons, Rules and Recipes.) This book is designed primarily for the patient.

†I wish to thank Miss Kathleen Ramsay for the care in which these determinations were performed.

TABLE 1

	Number of cases	Blood viscosity					
		High index		Low index		Fluctuant	
		Number	Per cent	Number	Per cent	Number	Per cent
Controls	37	14	38%	23	62%	2	5%
Cerebrovascular disease	36	34	94%	2	6%	28	77%

37 control subjects. In 26 subjects, the studies were made weekly (an average of 8 studies per subject), and, in 11 subjects, the repeated studies were made during a period of twenty-four hours (an average of 5 studies per subject). The control subjects varied in age from 21 to 73 years, the average age being 43 years. Similar repeated determinations were performed in 36 patients with clinically proved cerebrovascular disease (an average of 24 determinations per subject). These patients varied in age from 32 to 72 years, the average age being 61 years.

In the 37 control subjects, the viscosity index was relatively high in 14 and relatively low in 23 (see control panel in Figure 3). Frequent significant fluctuations in viscosity of 20% or more occurred in 2. In the 36 patients with cerebrovascular disease, the blood viscosity index was relatively high in 34 and relatively low in 2. In 28 cerebrovascular cases, the viscosity frequently fluctuated 20% or more from week to week (Table 1).

Effect of low fat diet on blood viscosity. The relationship of blood viscosity to hematocrit in selected control subjects not on diet is shown in Figure 1*a*, *b*, *c*, and *d*. In control subjects with relatively low blood viscosity, no significant change occurred in the viscosity when the low fat diet was consumed for up

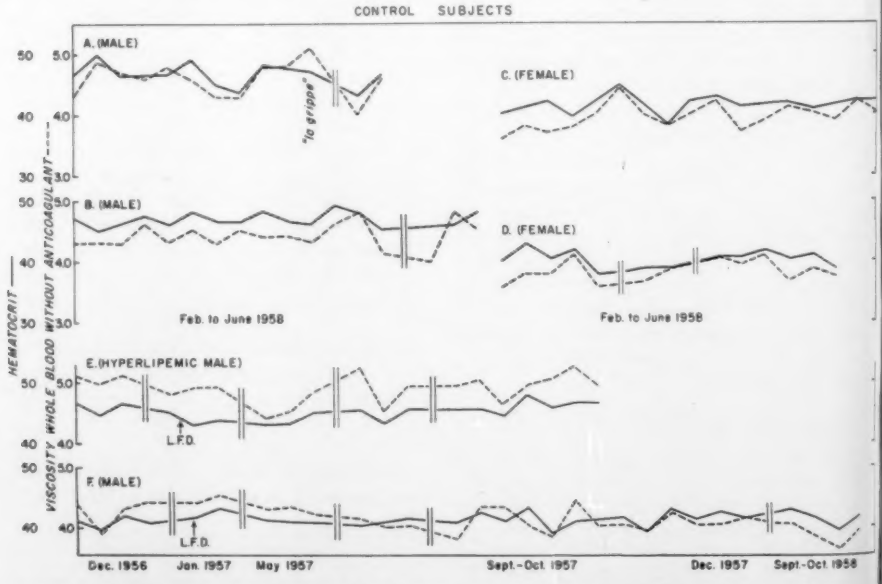

Fig. 1. Relationship of whole fresh blood viscosity (- - -) to the hematocrit (———) in a group of control subjects. Time in months and years is on abscissa; viscosity and hematcrit on ordinate.

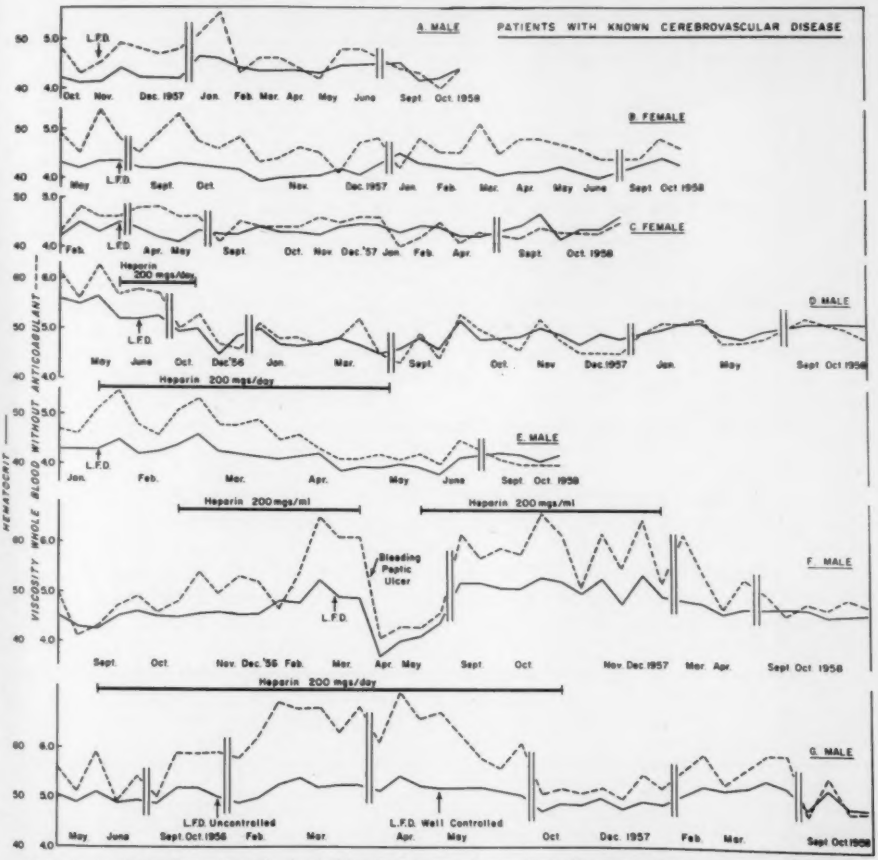
A. MALE
PATIENTS WITH KNOWN CEREBROVASCULAR DISEASE
L.F.D.
Oct. Nov. Dec. 1957 Jan. Feb. Mar. Apr. May June Sept. Oct. 1958
B. FEMALE
May L.F.D. Sept. Oct. Nov. Dec. 1957 Jan. Feb. Mar. Apr. May June Sept. Oct. 1958
C. FEMALE
Feb. L.F.D. Apr. May Sept. Oct. Nov. Dec. '57 Jan. Feb. Apr. Sept. Oct. 1958
Heparin 200 mgs/day
D. MALE
May June Oct. Dec.'56 Jan. Mar. Sept. Oct. Nov. Dec. 1957 Jan. May Sept. Oct. 1958
Heparin 200 mgs/day
E. MALE
Jan. Feb. Mar. Apr. May June Sept. Oct. 1958
Heparin 200 mgs/ml
Heparin 200 mgs/ml
Bleeding Peptic Ulcer
F. MALE
Sept. Oct. Nov. Dec.'56 Feb. Mar. Apr. May Sept. Oct. Nov. Dec. 1957 Mar. Apr. Sept. Oct. 1958
Heparin 200 mgs/day
G. MALE
L.F.D. Uncontrolled
L.F.D. Well Controlled
May June Sept. Oct. 1956 Feb. Mar. Apr. May Oct. Dec. 1957 Feb. Mar. Sept. Oct. 1958
VISCOSITY WHOLE BLOOD WITHOUT ANTICOAGULANT — HEMATOCRIT

Fig. 2. Relationship of whole fresh blood viscosity (- - -) to the hematocrit (———) in a group of patients with cerebrovascular disease. L.F.D. indicates point at which low fat diet was started. Time in months and years is on abscissa. Solid horizontal line indicates period of daily injections of heparin.

to fourteen months. In one control subject with relatively high blood viscosity (viscosity index 1.05), the blood viscosity began to fall slowly after being on diet about six months and reached its lowest point (viscosity index 0.93) after being on diet twenty-two months (Fig. 1*f*). In another subject with persistent hyperlipemia and relatively high blood viscosity, no significant fall in viscosity occurred during ten months on diet (Fig. 1*e*).

Thirty patients wtih cerebrovascular disease were placed on the low fat diet. Eleven were followed less than five months and have been included here only to help establish characteristic viscosity levels for the group. Nineteen patients were studied frequently for periods of six to thirty months. These will be discussed in more detail (Fig. 2).

The blood viscosity changed very little during the first three to six months on low fat diet. After this, the viscosity relative to the hematocrit decreased, and the weekly fluctuations

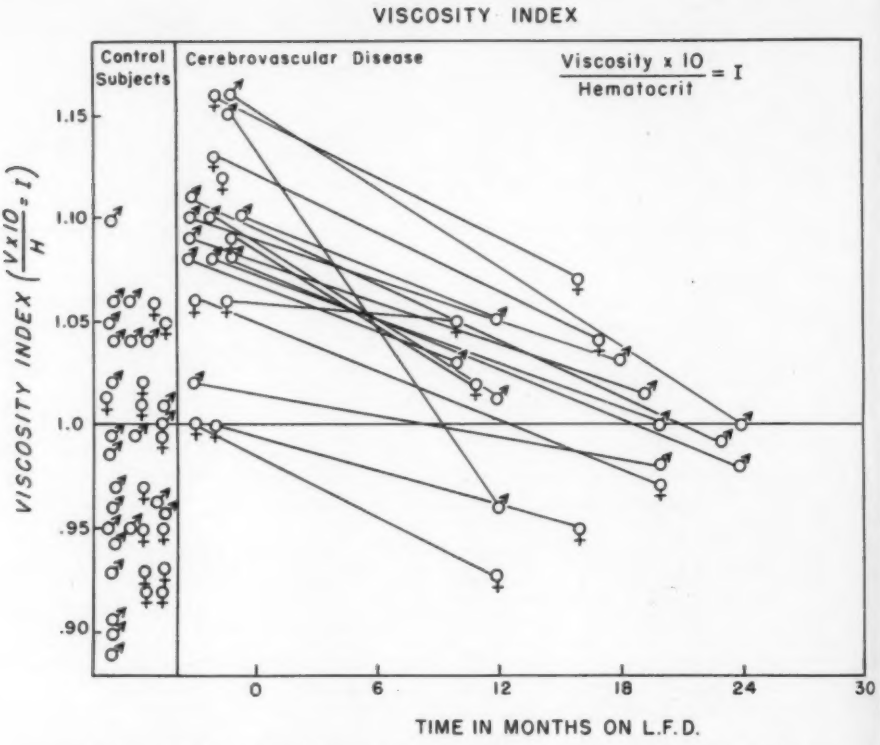

Fig. 3. Viscosity index in control subjects and in patients with cerebrovascular disease before and months after consuming low fat diet is shown.

became less marked and eventually came to reflect rather accurately the changes in the hematocrit (Fig. 2*a*, *b*, *c*, and *d*). This series of events occurred in 18 of our 19 patients who followed the diet with care during the period of observation. In 2 patients (Fig. 2*f* and *g*), the diet was at first poorly adhered to and the viscosity continued high and fluctuant. Subsequent rigid dietary control was followed by a slow fall in the viscosity index and stabilization of the viscosity. Shown in Figure 3 is the distribution of the viscosity index in our control subjects and in the 19 patients before and after being on the low fat diet for up to twenty-four months.

In 10 patients, heparin was also administered during the first two to six months on low fat diet (Fig. 2*d*, *e*, *f*, and *g*). It was injected subcutaneously by the patient once daily. A concentrated aqueous preparation* (200 mg. per cubic centimeter) was used in amounts sufficient to double or triple the clotting time six to eight hours after injection. The heparin appeared to influence the blood viscosity very little or not at all, since the viscosity remained high and fluctuant during the first several months that heparin was administered (Fig. 2*f* and *g*). The viscosity eventually decreased after the patient had adhered to the diet in excess of three to six months.

The buffy coat. In addition to the blood viscosity, extensive observations were made of the gross structure of the buffy coat in the hematocrit tubes. In experimental studies, we have observed that following fat meals the

*Furnished by Upjohn Chemical Co.

TABLE 2

	Control	*Cerebro-vascular disease*	*Diabetes with vascular disease of the retina*
Number of cases	17	28	5
Total number of bloods	231	692	104
Percentage number cases with ++ and +++ mixing	30%	93%	100%
Percentage ++ mixing (all bloods)	4%	18%	25%
Percentage +++ mixing (all bloods)	0.4%	10%	4%

buffy coat is often pink or red in color because of the presence of an admixture of varying numbers of red blood cells[17] instead of white and clearly demarcated from the underlying red blood cells. This is thought to be due to adhesiveness of the red blood cells. In the present clinical studies, slight admixture + at the junction of the buffy coat and red blood cells or mixture which involves less than the lower half of the buffy coat at any one point was considered "normal," since it was frequently observed in both control subjects and patients with cerebrovascular disease. Infiltration of the red blood cells above the middle of the buffy coat and below the upper three-quarter mark was considered ++ mixing, and infiltration of red blood cells from this point upward, +++ mixing.

In 17 control subjects studied weekly over long periods of time, ++ and +++ mixing occurred in but 5 and in only 2 of these controls did more than 10% of the blood samples show this degree of mixing of the buffy coat. On the other hand, 93% of our known cerebrovascular cases showed ++ and +++ mixing (Table 2). With the low fat diet, we observed no significant decrease in the number of bloods showing significant decreases of this mixing. In 5 patients with diabetes and early vascular disease of the retina, a similar mixing of the red blood cells with the buffy coat was observed.

Plasma viscosity. Plasma viscosity was not studied extensively. However, our few studies indicate a trend consistent with the rest of our data. The plasma viscosity in 26 control subjects taken at random averaged approximately 1.7, with a high of 2 and a low of 1.5. In 15 patients with cerebrovascular disease not on low fat diet, the average viscosity was 1.94, with a high of 2.1 and a low of 1.6. After their being on diet for approximately one year, the average plasma viscosity in 10 of the 15 patients with cerebrovascular disease was 1.75, with a high of 2 and low of 1.6.

Effects of physical activity on the blood viscosity. We have observed that several minutes of vigorous exercise increases both the hematocrit and viscosity in subjects free of clinical vascular disease. On the other hand, average or light activity seems to be followed by a fall in the blood viscosity. In hospitalized subjects free of symptomatic vascular disease, the viscosity is highest immediately after aris-

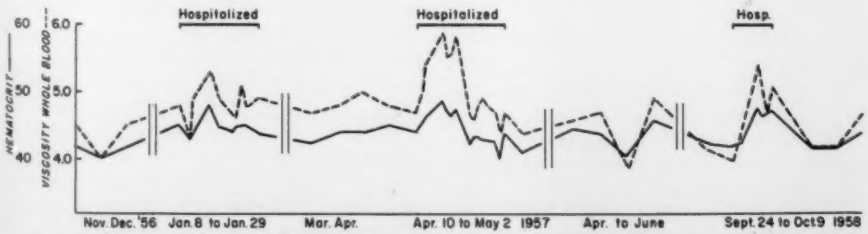

Fig. 4. Blood viscosity curve and hematocrit curves in patient admitted to hospital on 3 occasions for special studies. Note increase in viscosity during each hospitalization.

ing in the early morning and again late in the evening and is lowest during the middle of the day.[15] In the present study, the blood viscosity (and viscosity index) often rose sharply in our vascular cases when they were placed in bed or subjected to relative inactivity. One instance of this is shown in Figure 4. This patient with cerebrovascular disease was quite active outside the hospital. Three times he was brought into the hospital and placed at bed rest or semi-bed rest for viscosity studies. Each time while in the hospital, sharp rises were noted in his blood viscosity (and viscosity index).

Low fat diet in patients with diabetes and vascular disease of the retina. Five cases of diabetes with vascular disease of the retina (average age, 29 years) were studied on low fat diet for thirteen, eighteen, twenty-one, and twenty-two months, respectively.* In these cases, the blood viscosity was relatively high and fluctuant from week to week. In 3 cases on low fat diet, no change in blood viscosity occurred, in 2 of the cases, minimal decreases and stabilization of the blood viscosity was observed.

Clinical evaluation. In the course of our studies, 36 patients with cerebrovascular disease and 5 additional patients with diabetes and vascular disease of the retina were observed. Twenty-four of these patients were placed on the low fat diet and were observed for six to thirty months. Ten of them also received heparin for three to six months when first placed on the low fat diet. There was 1 death in a patient with diabetes and vascular disease. In addition, 1 patient with cerebrovascular disease continued to deteriorate slowly and relentlessly while on low fat diet plus heparin and 1 patient had a mild cerebral ischemic episode while on diet alone. The remaining patients remained active and ambulant.

Three patients had repeated transient cerebral ischemic episodes prior to treatment. One case was controlled successfully for four months first by heparin alone, then by heparin plus the low fat diet. The other 2 patients were placed on heparin and the low fat diet simultaneously and were free of ischemic episodes for four months. In all 3 cases, the heparin was then discontinued and no further ischemic episodes occurred while on the low fat diet alone for five to eighteen months. In general, our results with heparin appear to confirm previously reported studies indicating a salutary effect of anticoagulants on cerebrovascular disease.[18,19] It also appears that the low fat diet alone, after being consumed three to six months, was equally effective in controlling the ischemic episodes. It should be noted that the dangers from hemorrhage during anticoagulant therapy do not complicate treatment with the low fat diet. The author observed hemorrhage during treatment with heparin in 1 case not included in this series.

*Dr. John Harris referred these patients to us for study.

DISCUSSION

The relatively high blood viscosity observed in some control subjects and in all patients with cerebrovascular disease was probably due to their high fat intake, rather than to vascular disease itself. This is indicated by the significant reduction in blood viscosity which occurred after prolonged consumption of the low fat diet. It is surprising that such a uniform response of the blood viscosity to the low fat diet occurred. Concurrent studies on control subjects and on patients with diabetes indicated that the uniform decrease in blood viscosity was not a laboratory error. It is of interest that the intravenous injection of dogs with emulsified fat or lipemic chyle may cause a significant and sustained increase in blood viscosity.[20,21]

Because of the high factor of safety inherent in a normal vascular system, the increases in blood viscosity described in this paper probably would not have a sufficient effect on the circulation to cause significant tissue ischemia. It has been shown that animals can tolerate marked increases in blood viscosity resulting from large fat meals[20,21] or from injections of high molecular weight dextran.[22] Similarly well tolerated increases in blood viscosities have been observed in young human beings whose blood contained abnormal cryoglobulins and other abnormal large molecular weight globulins. With the development of atherosclerosis with narrowing of the vascular lumina, however, the circulatory factor of safety is reduced and eventually the point is reached

at which the circulation is critical. At this point, a relatively high blood viscosity or a sudden sharp increase in viscosity might cause a sufficient decrease in blood flow to result in tissue ischemia and infarction. It should be noted that marked fluctuations in viscosity occurred predominantly in patients with a high blood viscosity. Approximately 40% of our control subjects also had a relatively high blood viscosity. One wonders if they are not destined for early "occlusive" or ischemic vascular disease.

The cause of the increased whole blood viscosity in our cerebrovascular cases is due, partly at least, to increased viscosity of the plasma. On the low fat diet the plasma viscosity decreased to or near normal. This decrease in plasma viscosity was not accompanied by detectable alterations in the pattern of plasma proteins in paper electrophoresis,* although it is possible that unidentified changes in the proteins did occur.

In a discussion of whole blood viscosity, it is important that the physical state of the red blood cells also receive consideration. Aggregation of red blood cells in the circulation of the conjunctiva has been observed in patients with myocardial disease[23] and also in a number of our cases with cerebrovascular disease. Mixing of red blood cells throughout the buffy coat in many patients with vascular disease is probably an indication of adhesiveness of these blood elements and in turn an evidence of their tendency to form red blood cell aggregates.[17] There is considerable evidence to indicate that both the adhesiveness and aggregation of the red blood cells and mixing of the red blood cells with the buffy coat can be produced in both man and animals by high fat intake.[4–9,17]

Blood flow is laminar. Red blood cells and their aggregates tend to flow midstream surrounded by a layer of plasma. The increased resistance to flow produced by aggregation of red blood cells will vary both with the size of the aggregates and the diameter of the tubes in which they flow. Unless large, aggregates will cause a minimum of resistance to flow in tubes equal to or larger in size than arterioles or venules. As the aggregates increase in size, the resistance to flow will progressively increase. Large red blood cell aggregates were observed in the circulation of the cheek pouch of the hamster after fat meals,[5,6] and presumably this was one cause of the increased blood viscosity which was demonstrated in hamsters after fat meals.[7] In blood vessels smaller than arteriols and venules, relatively small aggregates will increase the resistance to blood flow. The degree of the circulatory slowing in this instance will be determined by the strength of the forces maintaining the aggregates. It appears that, unless the aggregates are very large, our viscosity measurements, performed with tubes approximately 300 μ. in diameter, will only partially reflect the resistance to flow which will be present in small arterioles and venules or in capillaries.

Surface tension measurements of the plasma and alterations in the shape of the red blood cells suggest that changes in the forces at the surface of the blood cells do occur after fat meals in animals and man.[4,17] It has been shown that in an electric field the migration of red blood cells in their own blood plasma is significantly slowed in patients with vascular disease.[24] On the other hand, if these same red blood cells are resuspended in saline, their migration is the same as the migration of red blood cells suspended in saline from suitable controls. This suggests that a reduction in negative (–) electrical charge had occurred on the surface of red blood cells from the patients with vascular disease. This could be a factor causing both increased adhesiveness and aggregation of the red blood cells. In this connection, it is interesting to call attention to the fact that, after large fat meals, the red blood cells of hamsters observed microscopically in the cheek pouch sometimes appeared to be enveloped by an amorphous film.[5,6] Further, in experiments with dogs which had been fed large fat meals, an opaque film sometimes coated our viscosity needles and pipettes and reduced their caliber. This material was not removed by alcohol or ether but was removed by papain, a proteolytic enzyme.[20,21] Such a material on the surface of red blood cells might well alter their electrical charge and the forces acting at their surfaces. It can be anticipated that this would alter the tendency of the red blood cells to aggregate.

*Extensive studies of plasma proteins by paper electrophoresis were made and revealed no significant changes.

Other physical changes, produced experimentally in the blood by large fat meals, which theoretically could hinder circulation and diffusion of oxygen to and from red blood cells have been discussed in detail in other papers.[4,17] These changes may cause little or no increase in the resistance of flow of blood in relatively large tubes, yet it seems likely that they might contribute significantly to the production of tissue ischemia.

It has been our observation that, if one hopes to reduce blood viscosity within the time limits observed in this study, slight or even moderate reduction in fat intake will not suffice. It is necessary to reduce the fat intake to or near the levels we have prescribed, and at least half of the lipid must be fluid at room temperature and contain a high percentage of highly unsaturated fatty acids.

SUMMARY AND CONCLUSION

In patients with cerebrovascular disease, the viscosity of fresh whole blood without anticoagulant and of plasma is usually relatively high. In addition, the viscosity of whole blood varies significantly. On low fat diet containing approximately 15 gm. of fat and 20 gm. of vegetable and fish oil, the viscosity, after a delay of three to six months, drops slowly to or toward normal.

The period of observation of patients on the low fat diet was up to thirty months. At the same time the viscosity becomes progressively more stable. There is also a marked tendency for the red blood cells to mix intimately with the platelets and white blood cells of the buffy coat in cerebrovascular cases. Similar mixing occurred in only an occasional control subject.

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Fate of red blood cells injected into cerebrospinal fluid pathways

John E. Adams, M.D., and Soewadji Prawirohardjo, M.D.

ALTHOUGH CEREBRAL HEMORRHAGE occurs frequently, little is known about the mechanisms by which extravasated erythrocytes are eliminated from the subarachnoid space. In 1930, Sprong[1] studied by means of consecutive lumbar punctures the rate of disappearance of erythrocytes from the cerebrospinal fluid in 15 patients with traumatic subarachnoid hemorrhage. He found that five to six days after a single episode of bleeding, red blood cells could no longer be found in the spinal fluid. Using the same technic, he then demonstrated the same rate of disappearance of erythrocytes from the cerebrospinal fluid when 2 cc. of autogenous blood was injected into the cisterna magna of dogs.

Complete drainage of the entire volume of cerebrospinal fluid one hour after cisternal injection of 2 cc. of autogenous blood resulted in recovery of only 30% of the injected blood. Sprong assumed, therefore, that, as early as one hour after a subarachnoid hemorrhage, the red cells that remained in the cerebrospinal fluid represented only a fraction of those extravasated. He hypothesized that the remaining red blood cells were quickly bound in a clot or became entangled in the meshes of the arachnoid trabeculae.

This concept was extended by Hammes[2] and Jackson,[3] who emphasized the role that phagocytic cells arising in the arachnoid played in the elimination of extravasated erythrocytes from the cerebrospinal fluid in human beings and dogs.

Simmonds,[4] however, studied the same problem in rabbits and cats and concluded that phagocytosis of erythrocytes is minimal for at least twenty-four hours after the injection of autogenous blood into the cerebrospinal fluid pathways. He found that, in these 2 species of animals, injected erythrocytes began to leave the subarachnoid space one to three hours after the injection and that most erythrocytes had disappeared within forty-eight hours.

Simmonds could find no evidence of clotting of the injected blood and concluded that the red cells passed quickly through the cerebral meninges, appeared in the deep cervical lymph duct, and subsequently appeared in the retroorbital tissues and cervical lymph nodes. Simmonds was of the opinion that, in rabbits and cats, the principal routes of absorption of extravasated blood from the cerebrospinal fluid pathways are through the arachnoid sheath of the optic nerves and through the meningeal investments of the olfactory filaments and then into the lymphatic system. He also found that the red cells were absorbed directly into the blood stream via the arachnoid villi but that this route was of secondary importance.

Probably, the process of elimination of extravasated blood from the cerebrospinal fluid may vary in different species. The present study was designed to investigate this problem with the use of newer technics—with particular reference to the concept that red blood cells can be absorbed from the cerebrospinal fluid pathways in the intact state.

Method. Mongrel dogs were utilized for this study: 10 cc. of blood from each animal was tagged with 100 to 200 μc. of CR^{51} by adding 0.5 cc. of a solution of sodium chromate ($Na_2 Cr^{51} O_4$) and thoroughly mixing for forty-five minutes. By this method, a stable

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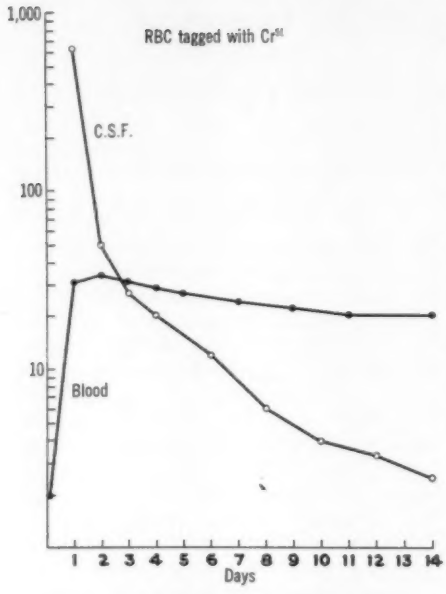

Fig. 1. Pooled data from 12 experiments plotted on semilog paper. The ordinate is the per cent of total injected dose in counts per second.

tag of the hemoglobin by Cr^{51} was achieved. The plasma was then separated by centrifugation, and the packed cells were washed 3 times with normal saline solution. A 2 cc. aliquot of the suspended red cells was then diluted to 100 cc. The cisterna magna of the animal was then injected with 6 to 10 cc. of this suspension; 1 cc. was kept as a standard for subsequent comparison with the specimens taken for Cr^{51} measurement. Samples of cerebrospinal fluid obtained by cisternal punctures and samples of venous blood were analyzed for Cr^{51} tagged red cells. In a scintillation counter, 2 cc. samples were counted with a thallium-activated sodium iodide (Na I) crystal. Of the gamma rays emitted, 15% were observed as counts. Venous blood samples were obtained two hours after injection, and daily samples were obtained thereafter. The specimens of cerebrospinal fluid were obtained on either the first or second day after injection and on alternate days thereafter.

RESULTS

Blood studies. The data were pooled, and nearly uniform curves were obtained in each of 12 dogs studied. In the two-hour specimen, 2 cc. samples of blood contained an average of 0.002% of the total injected dose, ranging between 0.001 and 0.004%. At the end of twenty-four hours, an average of 0.031% of the total dose was found in a 2-cc. sample of venous blood. The maximum activity was found after forty-eight hours. The highest rate of absorption, however, occurred within the first twenty-four hours (Fig. 1). Thus, by far the greatest amount of transport of Cr^{51}-labeled cells from the subarachnoid space to the blood occurred in the first forty-eight hours after injection. These data agree closely with the data obtained in the examination of the cerebrospinal fluid, as will be shown later.

In the two-hour blood samples, all of the Cr^{51} was evidently in intact erythrocytes, since examination of the plasma, after separation of cells in the same samples by centrifugation, revealed no activity. In the twenty-four-hour samples, from 1.5 to 3% of the total sample count appeared in the plasma. The amount increased slightly each day until the fourth to sixth day, when again no Cr^{51} could be found in the plasma.

We assumed, therefore, that intact, tagged red cells were absorbed from the subarachnoid space into the blood stream and that significant hemolysis does not occur. This assumption is valid if it can be shown that no Cr^{51}, which might be liberated from hemolyzed blood in the cerebrospinal fluid and subsequently absorbed into the blood, can be incorporated into other erythrocytes already circulating in the blood stream. In this regard, Ebaugh[5] found that intravenously injected hemoglobin tagged with Cr^{51} was not incorporated into circulating red blood cells for at least one month and also that radiochromium released from hemolyzed transfused erythrocytes cannot be incorporated into the recipient's own red blood cells.

To investigate this point further, we injected hemolyzed blood tagged with Cr^{51} into the cisterna magna of 2 dogs and examined samples of venous blood at the same time intervals as in the previous series of dogs. The samples showed maximum counts of less than

0.01% of the total injected dose at twenty-four hours. Separate examination of blood plasma and packed cells in these 2 experiments revealed that all of the radioactivity was contained in the plasma. The time relationships of the disappearance of Cr^{51} in the whole blood samples of dogs injected with hemolyzed blood corresponded with the disappearance of radioactivity in the blood plasma of dogs injected with tagged erythrocytes. This supports the assumption that the slight degree of radioactivity found in the plasma of dogs injected with intact erythrocytes originates from the absorption of hemolyzed blood from the subarachnoid space but that the amount of hemolysis is, in fact, insignificant.

Although blood volumes were not measured in these experiments, using an average figure of 1,200 cc., it can be calculated that 20% of the total injected dose of Cr^{51} is present in the circulating blood after twenty-four hours.

Cerebrospinal fluid studies. Samples of cerebrospinal fluid were obtained at the end of twenty-four and forty-eight hours and on alternate days thereafter. The twenty-four-hour samples of cerebrospinal fluid contained an average of 0.62% of the total injected dose. At the end of seven days, only 0.002% remained in the cerebrospinal fluid sample. Using Sprong's figure of 11 cc. for the total volume of cerebrospinal fluid in the dog, it again can be calculated that at the end of twenty-four hours, 3.4% of the total injected dose of Cr^{51} remains in the cerebrospinal fluid. At the end of forty-eight hours, this figure drops to 0.28%. These data support the conclusion drawn from the blood studies that by far the greatest proportion of tagged cells disappears from the cerebrospinal fluid within forty-eight hours after injection (Fig. 1).

DISTRIBUTION OF Cr^{51} FORTY-EIGHT HOURS AFTER CISTERNAL INJECTION
Mean value of 5 experiments

	Per cent of total injected dose
Blood	24.2
Cerebrospinal fluid	1.5
Brain, meninges, and spinal cord	73.2
	98.9

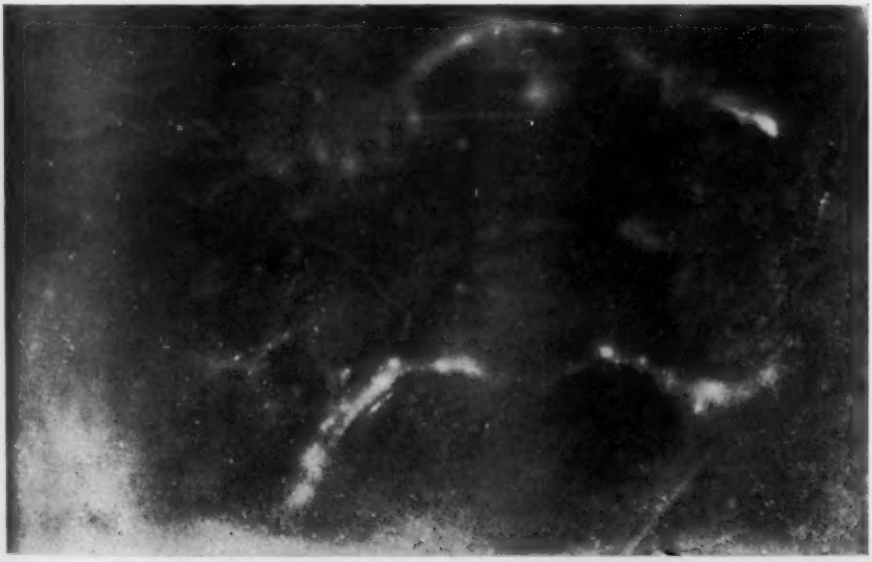

Fig. 2. Radioautograph of coronal section of brain removed six days after cisternal injection of 100 μc. of Cr^{51}. The exposure time was fifty-six hours. Negative print: Cr^{51} deposit appears in white.

The above data indicate that, at the end of twenty-four hours, 20% of the total dose of Cr^{51} injected into the cerebrospinal fluid can be recovered from the blood stream, while 3.4% remains in the cerebrospinal fluid; the Cr^{51} remains incorporated in the tagged erythrocytes without the occurrence of significant hemolysis.

Where is the remaining 76.5% of the injected Cr^{51} distributed? Possibly, a far greater amount of the injected red cells is quickly absorbed into the blood stream and then distributed to other tissues of the body—in spite of the fact that the radioactivity found in the blood remains at a prolonged plateau after reaching a maximum in forty-eight hours.

Wennesland and associates[6] have shown, however, that there is little, if any, sequestration of tagged red cells reinjected into the circulating blood. It seemed possible, therefore, that the remaining three-fourths of the injected, tagged red cells remained somewhere in the cerebrospinal axis and were not absorbed. To investigate this point, the same studies were done on 5 more dogs, with the addition that, at the end of forty-eight hours, the cerebrospinal fluid was drained from each animal and analyzed for Cr^{51} (see table).

At the same time, the brain, spinal cord, and surrounding meninges were removed and similarly studied. The results indicated that 98.9% of the total injected dose can be accounted for and that the previously unaccounted for 73.2% of the injected dose resides in the brain, cord, and meninges. Radioautographs of specimens taken six days after the injection of tagged erythrocytes demonstrated the presence of considerable radioactivity still confined to the arachnoid (Fig. 2).

We agree, therefore, with Sprong's original conception that, in the dog, the major portion of extravasated blood in the cerebrospinal fluid becomes enmeshed and fixed in the arachnoid trabeculations. The remaining 25% of the injected cells are absorbed directly into the blood stream. How this is accomplished remains a matter for speculation. It seems surprising that a structure as large as an intact erythrocyte can pass the cerebrospinal fluid-blood barrier. Yet, a direct absorption into the blood stream in these experiments appears probable, since examination of the cervical lymph nodes and lymph obtained from the cervical lymph duct during the first twenty-four hours after injection of tagged erythrocytes into the cisterna magna failed to reveal any radioactivity, thus apparently eliminating the lymphatic system as a route of absorption.

If as much as 75% of the blood which may be extravasated into the cerebrospinal fluid in an intracranial hemorrhage becomes enmeshed in the arachnoid trabeculae, obstruction of the absorptive bed may easily result. In this manner, a reasonable explanation is provided for the development of communicating hydrocephalus which has been reported by Foltz and Ward[7] to follow subarachnoid hemorrhage.

SUMMARY

The distribution of tagged red blood cells injected into the cisterna magna of dogs has been studied. Our findings indicated that, of the total injected dose of erythrocytes, approximately 25% is absorbed directly into the blood stream in an intact state. Insignificant hemolysis occurs. The remaining 75% of the injected red cells become enmeshed and fixed in the arachnoid. This experimental finding may explain the occurrence of communicating hydrocephalus following subarachnoid hemorrhage by obstruction of the normal absorptive mechanism.

We would like to express our appreciation to Professor Kenneth G. Scott and to the Radioactivity Research Center of the University of California School of Medicine for assistance and facilities.

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On the existence of the cerebral type carotid sinus syncope

George L. Engel, M.D.

IN A RECENT PAPER, "On the Nonexistence of the So-Called Cerebral Type of Carotid Sinus Syncope," Gurdjian and associates[1] commit themselves to the position that there is no such syndrome. Instead, they claim, the syndrome is an artifact occurring in patients with partial or complete occlusive cerebrovascular disease involving the contralateral carotid, contralateral anterior cerebral, or the basilar-vertebral systems. In these patients, massage of the carotid sinus apparently results in compression of the carotid artery sufficient to reduce blood flow to the brain to the point of ischemia.

Studying 100 patients who exhibited syncope on carotid artery compression, Gurdjian found 76 to have angiographic evidence of such occlusive cerebrovascular disease. In all 76, an ischemic response was shown to be responsible for, or included in, the syncopal reaction. The remaining 24 patients manifested other types of syncope, including cardioinhibitory carotid sinus syncope and vasodepressor syncope. Among 154 patients without cerebrovascular disease, only 10 showed syncopal symptoms on carotid artery compression; in 2 of these, the syncope was secondary to asystole. The authors do not state clearly whether the carotid sinus per se was stimulated nor exactly what portion of the carotid artery was compressed. Nor is it mentioned whether the patients were examined in the standing, sitting, or recumbent position, a matter especially important in the evaluation of vasodepressor responses.

This study clarifies a precaution necessary in the diagnosis of cerebral carotid sinus syncope, a precaution that, moreover, was clearly alluded to by Weiss[2] in his original publications as well as by others.[3,4] It cannot be considered as evidence for the "nonexistence" of the cerebral type of carotid sinus syncope. For one thing, the authors apparently did not investigate any patients with the complaint of syncope but only patients among whom syncope was produced by occlusion of one carotid sinus. Hence, the probability of their series including patients with true cerebral-type carotid sinus syncope was greatly reduced. In the second place, they apparently did not examine the carotid sinus and artery separately; hence, they could not be expected to discover patients who reacted to carotid sinus massage but not to carotid artery compression. Needless to say, the former must be done gently and be of an intermittent character lest the artery also be occluded.

More important, however, in refuting the authors' conclusions are the data on the proved cases of cerebral-type carotid sinus syncope. In 5 cases reported by Weiss,[3] the syndrome was abolished temporarily when the tissues around the sensitive carotid sinus were infiltrated with 1% Novocain. A similar, much more prolonged effect was achieved after section of the carotid nerve.[3] Further, it is general experience that sensitivity of the carotid sinus is quite variable, so that at some times syncope is readily provoked by very brief, gentle pressure while at other times even prolonged, vigorous massage is without effect.[2-4] During sensitive periods attacks may be brought on by movements of the head and neck which would be most unlikely to interfere with cerebral blood flow. These last two clinical points seem hardly compatible with

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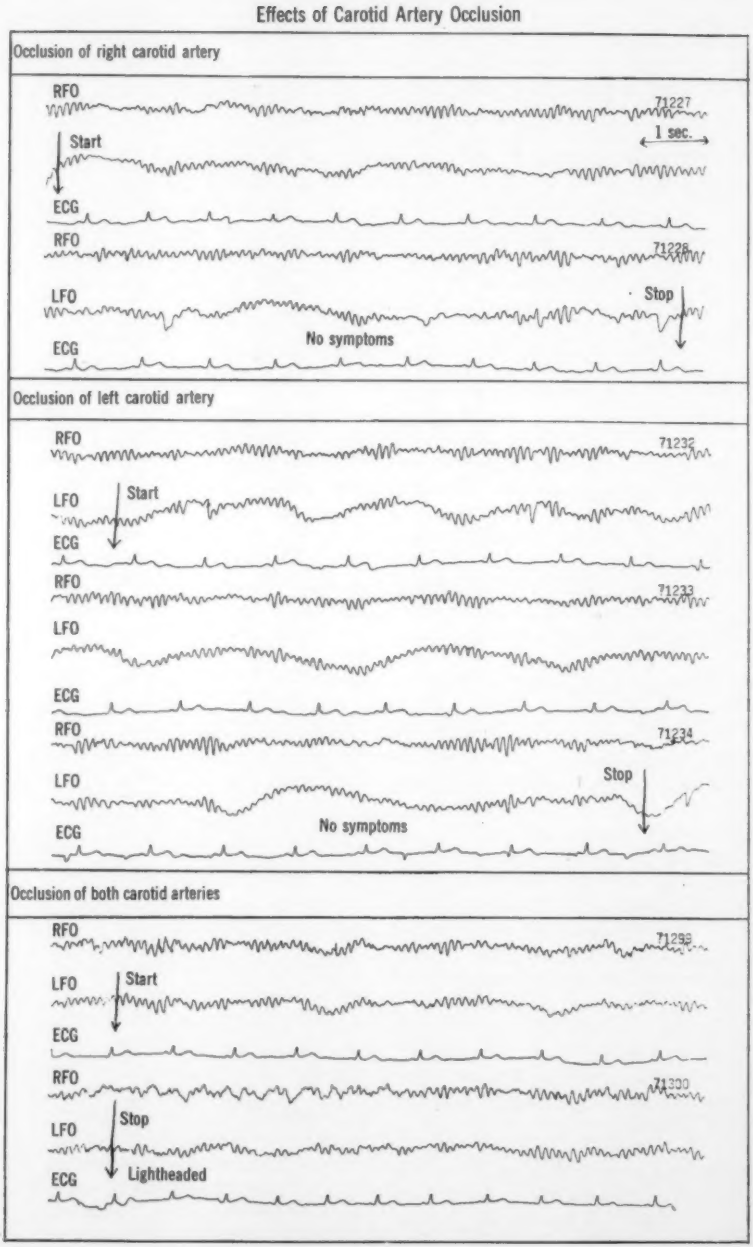

Figure 1. Carotid artery occlusion

the notion of occlusive cerebrovascular disease being responsible. The age incidence, involving as it does a predilection for young adults, also seems against this theory.

The conclusive evidence, however, is the demonstration that, in cerebral-type carotid sinus syncope, sinus massage produces both symptoms and corresponding focal electroencephalographic changes, while unilateral carotid artery occlusion produces neither.[4,5]

The 2 patients studied in most detail were young men 28 and 36 years old, respectively. Both had experienced many spontaneous attacks of syncope, usually on turning the head. Each carotid artery was occluded 20 seconds without producing either symptoms or electroencephalographic changes. When both carotid arteries were occluded simultaneously, symptoms of lightheadedness and bilateral electroencephalographic slowing began within 10 seconds (Fig. 1). In contrast, stimulation of each carotid sinus in the recumbent position led within 10 seconds to contralateral symptoms of numbness, tingling, and clonic jerks and to ipsilateral electroencephalographic slowing (Fig. 2). There were no significant changes in pulse or blood pressure. This is clearly illustrated in the accompanying figures.

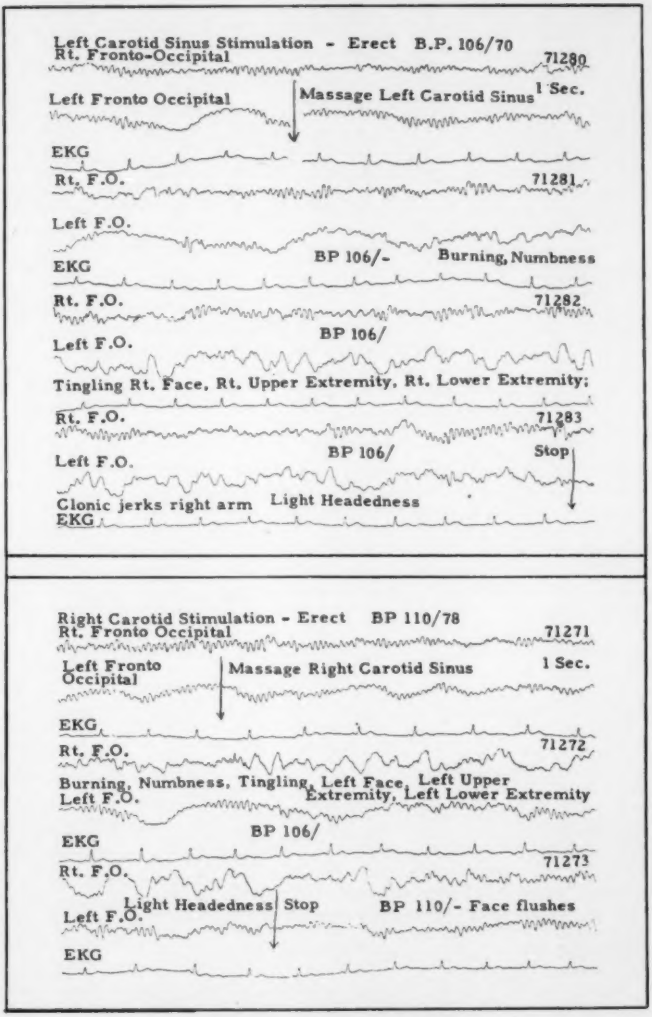

Figure 2. Carotid sinus stimulation

The diagnosis of cerebral-type carotid sinus reflex hypersensitivity is fraught with error unless several precautions are taken in the examination of the patient. Gurdjian's work points up one source of error. Because the requirements for diagnosis are apparently not well known, I reproduce below directions for examination which were published in 1950:[4]

Stimulation of the carotid sinus may be misleading in three important respects and caution in the interpretation of results cannot be too strongly emphasized. In the first place, a coincidental carotid sinus hypersensitivity may be regarded as being more important than it actually is. Carotid sinus reflex hypersensitivity is relatively common, while carotid sinus syncope is infrequent. The second source of error lies in confusing hysterical syncope with the cerebral type of carotid sinus response. The third error results from carotid artery occlusion when too firm pressure is applied, particularly when stimulation is bilateral.

The carotid sinus is best located by identifying the common carotid artery by its pulsation at about the level of the thyroid cartilage and posterior to the anterior belly of the sternocleidomastoid muscle. The artery is then traced upward until the bulge at the bifurcation is felt. With the head of the patient turned slightly away from the examiner, two fingers are inserted medial to the artery, which is retracted laterally. Simple pressure or an up and down massaging motion may now be applied. The latter is preferred because there is less possibility of producing an artifact by obstruction of carotid blood flow, resulting in cerebral ischemia. With this technique, the carotid sinus is not likely to slip out from under the examiner's fingers during the stimulation, a common reason for failure to elicit a response from a hypersenstitive carotid sinus.

The patient should always first be examined in the recumbent position. This is suggested, not only because it is more informative when done in this way, but also because it is safer. In the literature there are several reports of accidents, including a fatal one, following carotid sinus stimulation in the erect position (sitting or standing) in older people. One should never stimulate both carotid sinuses simultaneously.

The first maneuver, with the patient recumbent, is to *massage some portion of the neck other than the carotid sinus.* If the patient faints without change in pulse and blood pressure, the diagnosis is almost certainly hysterical syncope. The importance of doing this first cannot be overemphasized because otherwise one may have great difficulty in distinguishing a cerebral type of response from an hysterical response.

The second step is to stimulate each carotid sinus in turn while auscultating the heart. Some bradycardia is normal, while asystole of three seconds or longer is abnormal. Asystole of at least five seconds duration is necessary to produce syncope while standing. Much longer asystole may occur without symptoms in the recumbent position. If syncope occurs and there is no asystole or asystole is too short, the diagnosis of cerebral type of carotid sinus reflex hypersensitivity is suggested. The occurrence of focal neurological manifestations and electroencephalographic changes during the faint will further favor such a diagnosis. A depressor reflex will not cause syncope in the recumbent position.

If asystole occurred, the patient may then be given atropine, 0.0012 Gm. (gr. 1/50) subcutaneously and re-examined in 30 minutes or 0.001–0.0008 Gm. (gr. 1/60–1/75) intravenously and re-examined in five minutes. If now no symptoms and no slowing of the heart occur in either the recumbent or erect position, the vagal type of carotid sinus reflex hypersensitivity is established. Vagal reflexes may be eliminated for twenty-four hours or more following this amount of atropine. If syncope occurs in the recumbent position after atropine and there is now no change in pulse and blood pressure, the cerebral type of response is indicated. If syncope occurs now only in the standing position, the depressor type of response is suggested and this may be proved by recording the blood pressure simultaneously. Two or even three types of hypersensitivity may occur together, but such combinations can still be distinguished by this method of examination, for atropine will eliminate the vagal response and the recumbent posture will minimize the depressor response. The cerebral response can only be eliminated by local anesthetization of the carotid sinus.

When the diagnosis of a cerebral type of response is indicated, a final control should be occlusion of the common carotid artery below the carotid sinus. When inadequate collateral circulation is present, symptoms may result merely from incidental occlusion of the carotid artery during stimulation. Patients with the cerebral type of response do not develop any symptoms on occlusion of the carotid artery alone.

CONCLUSIONS

The cerebral type of carotid sinus syncope is a well established, although uncommon syndrome. However, it may readily be confused with cerebral ischemia due to cerebral artery occlusion in the presence of cerebrovascular disease and with hysterical syncope, unless proper precautions are taken.

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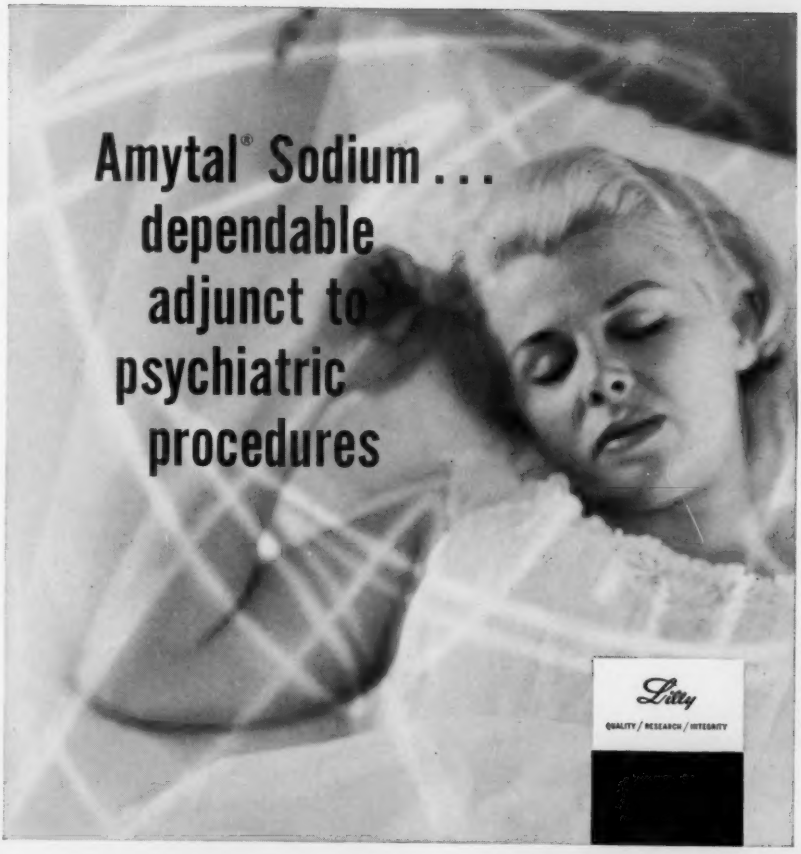

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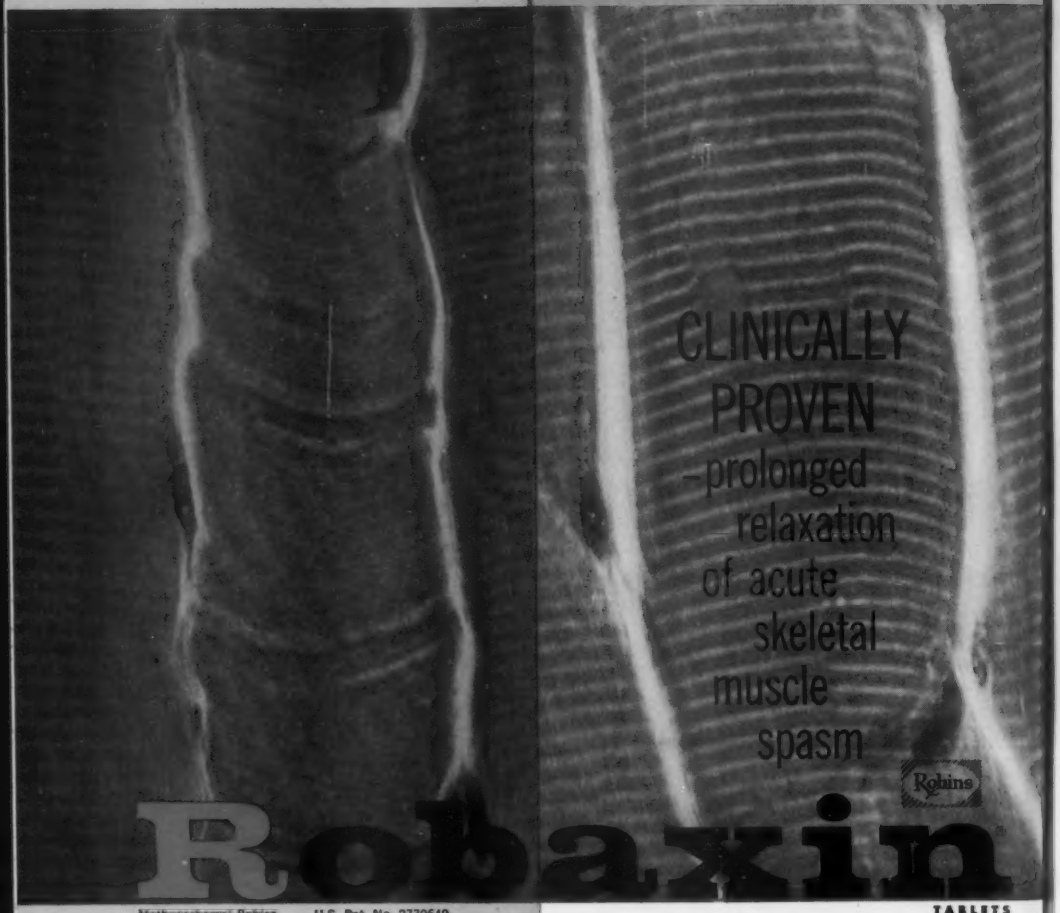

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Forsyth[2]	58	"pronounced" 37	20	—	1
Lewis[3]	33	"good" 25	6	—	7
O'Doherty & Shields[4]	17	"excellent" 14	2	1	0
Park[5]	30	"significant" 27	—	2	1
Plumb[6]	60	"gratifying" 55	—	—	5
TOTALS	236	184 (78.0%)	34 (14.4%)	4	14

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Diuril, HydroDiuril, and Diupres are other antihypertensive drugs originated by Merck Sharp & Dohme.

OBESITY AND WEIGHT REDUCTION

White males are twice as likely to become overweight as females of the same race, according to Parke, Davis & Co. of Detroit, Mich. Among nonwhite persons, however, obesity—weight at least 20% more than normal—is more prevalent among women. About one-fifth of all adults in the United States are overweight, about 7% are obese.

Height-weight tables are not the best guide for determining obesity. Excess subcutaneous fat should be estimated by specific gravity and skin-fold measurements.

A long-term approach yields the best results in dieting. When a person maintains a normal weight for six months to a year after weight reduction, it is likely that weight will be kept down for a long time. As many as 80% of obese patients who begin a reducing program may stop for one reason or another. Among obstacles encountered by would-be dieters is a complex of emotional reactions termed "dieting depression," which hampers progress in 54% or more of cases.

In 100 dieting, obese patients in a nutrition clinic, weakness and nervousness were the most common unpleasant reactions; each was reported by about 21% of patients. Other symptoms were irritability, fatigue, and nausea.

$10,000 GRANT FROM LILLY

Lilly Endowment, Inc., Indianapolis, has granted $10,000 to Carleton College, Northfield, Minn.

The funds will be used for academic improvement of faculty members in a two and one-half year period. Carleton will support 14 faculty members in doctoral and postdoctoral study in humanities and social sciences.

(Continued on page 25A)

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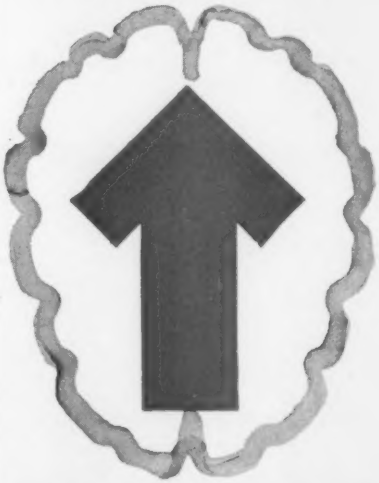

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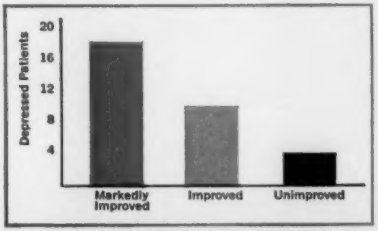

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To facilitate psychotherapy in the emotionally disturbed child, and to enable him to lead a stable life during such therapy, adjunctive treatment with PROZINE is often advantageous. In reporting on 176 disturbed children who received PROZINE, Ehrmantraut et al.[1] found that 85.8 per cent showed moderate to marked improvement in behavior reactions and adjustment to institutional care.

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1. Ehrmantraut, W., et al.: Scientific Exhibit Presented at the District of Columbia Medical Society Meeting, Nov. 24, 1958, Washington, D.C.

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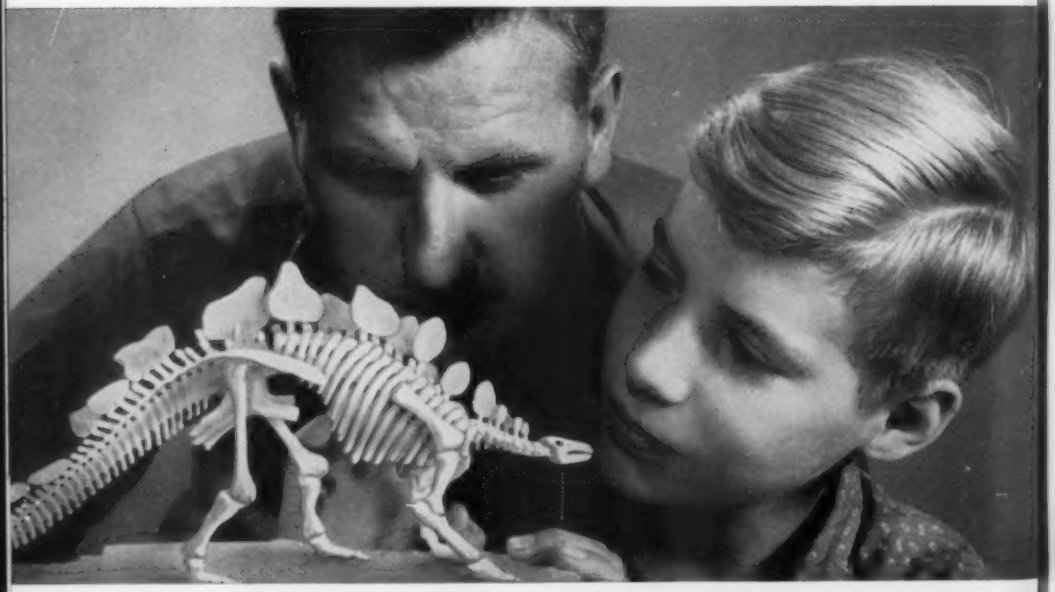

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(Continued from page 23A)

NEWLY-RELEASED TRANQUILIZING AGENT

A highly active tranquilizer made by Smith, Kline & French Laboratories, Philadelphia, trifluoperazine (Stelazine), is being released in 1-mg. tablets in bottles of 50 and 500.

When given in low doses—2 to 4 mg. daily—the drug calms agitation and tension and, at the same time, relieves apathy, listlessness, and emotional fatigue in patients with anxiety and restores an alert, more confident outlook and normal drive in apathetic patients.

Stelazine is often effective when other tranquilizers fail. Normal acuity, alertness, and natural sleep patterns are restored in many patients. Symptoms are relieved within twenty-four to forty-eight hours; duration of activity is more than twelve hours.

Side effects, such as drowsiness, dizziness, or stimulation, are infrequent, slight, and transitory. Neither jaundice nor agranulocytosis has been reported. The feeling of indifference resulting from use of other tranquilizing agents does not occur.

Chronic schizophrenic patients, considered hopelessly withdrawn, have improved with high doses of 10 to 40 mg. daily.

ANIMAL STUDIES IN CARDIOVASCULAR DISEASE

Finding animals most likely to yield important new information about heart and blood vessel disease is a major challenge to the research scientist. Dr. John L. Schmidt of Abbott Laboratories, North Chicago, Ill., states that, while man's cardiovascular system is not exactly like that of a chicken, rat, or dog, some reactions are similar. Ultimately, the greatest useful knowledge of cardiovascular problems will result from experiments with many different species.

For example, explains Dr. Schmidt, atherosclerosis in rabbits and chickens resembles human atherosclerosis; yet, interesting differences occur between each animal and the human being and even between the 2 animals.

Administration of benzhydryl piperazines and related compounds lowers blood cholesterol values in mice and dogs, but has no effect in chickens and very little effect in rabbits. Action of the compounds in man has not yet been proved.

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S.A.Vite, a sustained-action multivitamin tablet, is now available from Ayerst Laboratories, New York City. By controlled release, a single administration provides benefits previously obtainable only via divided dosage. Ideal multivitamin support, wherever nutritional therapy is indicated, is obtained with 1 tablet daily, preferably at breakfast. The tablets are available in bottles of 60 and 500.

(Continued on page 27A)

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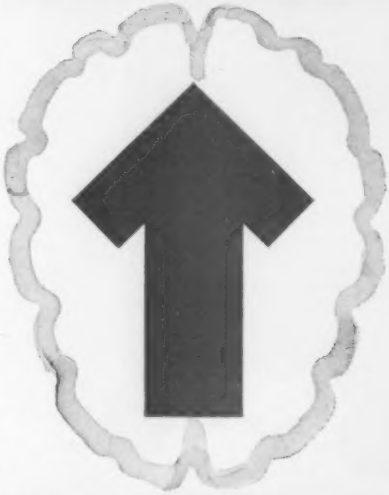

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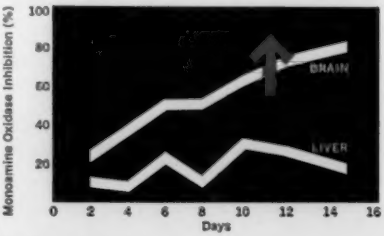

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PRODUCTS AND SERVICES

(Continued from page 25A)

SOMA FOR CEREBRAL PALSY PATIENTS

Soma, a drug made by Wallace Laboratories, New Brunswick, N. J., and used for pain relief and muscle and joint stiffness, is safe and useful for cerebral palsy patients, states Dr. Winthrop Morgan Phelps, founder of the Children's Rehabilitation Institute for Cerebral Palsy, Baltimore.

Of 43 cerebral palsy patients given Soma orally twice daily for four months, 88% of the spastic and 55% of the rigidity cases were benefited.

Braces could be tolerated comfortably for a longer period of time and ability to accept physical therapy was improved, Dr. Phelps observed. Soma appears to be superior to any other drug now available for relief of spasticity and rigidity under similar conditions, he said.

Lethargy and occasional drowsiness were the only undesirable effects noted in the patients.

HIGHLY EFFECTIVE ANTIDEPRESSANT

Depression caused by dysfunction within the patient's body — as opposed to those resulting from outside events, such as death of a loved one, loss of money, etc. — may be relieved by treatment with phenalzine dihydrogen sulfate (Nardil), made available by the Warner-Chilcott Laboratories. Dr. L. Earle Arnow, of the Warner-Lambert Research Institute, Morris Plains, N. J., reported to the June 6 meeting of the American Therapeutic Society that Nardil was effective in 84% of 580 treated patients. Improvement was noted within a week, maximum benefit occurred several weeks later.

No toxicity occurred, and no clinical or laboratory evidence of liver, kidney, or other organ damage was observed, stated Dr. Arnow.

INTRODUCTION OF AEROSOL SURFACAINE

Cyclomethycaine (Surfacaine), a topical anesthetic, has been made available by Eli Lilly and Company, Indianapolis, as an aerosol.

The fine dispersion of the anesthetic in this form coupled with prompt superficial absorption gives almost instant relief of topical pain and discomfort, that persists for several hours. Application by aerosol saves time, eliminates waste, prevents contamination, and obviates direct contact with affected areas.

Aerosol Surfacaine should be applied three or four times daily and is useful for skin abrasions, thermal and chemical burns, pain and itch of the vulvar and anal areas, postsurgical wounds, insect bites, and contact dermatitis.

Incidence of allergic reactions to Surfacaine is low. The anesthetic has been used to cover as much as two-thirds of the body in some burned patients without any undesirable effects.

(Continued on page 28A)

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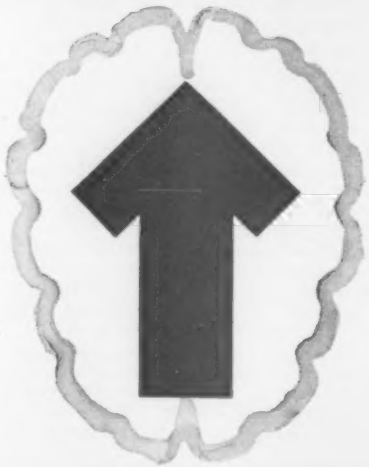
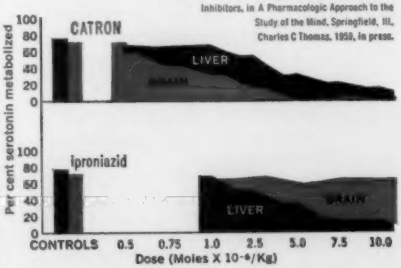


Elevates mood, brightens outlook by raising levels of mood-controlling neurohormones, serotonin and norepinephrine... at doses which have little or no effect on the liver.

Horita, A.: The Pharmacology of the Monoamine Oxidase Inhibitors, in A Pharmacologic Approach to the Study of the Mind, Springfield, Ill, Charles C Thomas, 1959, in press.



Lakeside Laboratories, Inc. Milwaukee 1, Wisconsin

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PRODUCTS AND SERVICES

(Continued from page 27A)

NORDSON SPONSORS SYMPOSIUM

A one-day symposium on "The Evaluation of New Drugs" was held in Philadelphia at the Albert Einstein Medical Center. Nordson Pharmaceutical Laboratories, Irvington, N. J., underwrote the meeting.

Opening the symposium, Dr. P. F. Lucchesi, executive vice-president and medical director of the Center, said, "I think it is a good thing that many effective drugs are being produced, but this places a new responsibility upon the medical profession. It is duty bound to evaluate these new drugs with rigid discipline."

Dr. Harold S. Feldman of New York Medical College, New York City, said that general physicians were in a position to discover problems about side effects, dosage, and administration of new drugs that cannot otherwise be anticipated.

In another speech before the Symposium, Dr. Dale Friend of the Harvard University Medical School, Boston, estimated that 40 to 50 new compounds are produced each year for testing on patients and that another two dozen require screening as anticancer agents. These circumstances underline the need for careful selection of physicians, patients, and technics in testing new pharmaceuticals, he said.

Dr. Friend recommended that young patients be chosen for new-drug testing whenever possible, because the absence of complications and deteriorative disease in such subjects made precise drug evaluation more feasible than in older people.

Also at the Symposium, Dr. John H. Moyer and Dr. Joseph R. DiPalma of Hahnemann Medical College and Hospital, Philadelphia, discussed critical attitudes in medical education.

Dr. Walter Modell of New York Hospital and Cornell University Medical College, New York City, presented reliable technics for use in evaluation of new drugs on patients.

USE OF HYPAQUE (WINTHROP) IN CEREBRAL ANGIOGRAPHY

Clear, well-defined silhouettes were produced in each of 100 patients during angiography performed with the contrast agent Hypaque, a product of Winthrop Laboratories, New York City. Dr. Robert A. Kuhn, Morristown, N. J., states that the results had considerable diagnostic value and that the angiograms were made with complete safety to the patients.

Roentgenograms demonstrated that the cerebral vascular tree filled with Hypaque permitted more accurate diagnosis of both the common and uncommon types of brain dysfunction.

Dr. Kuhn's studies accentuated the frequent large discrepancies between clinical and anatomic diagnoses of patients with stroke. It was also established that "a variety of lesions have the capacity to produce clinically similar states of cerebral neurologic dysfunction." Thus, Dr. Kuhn points out, cerebral angiography is an extremely valuable method of managing brain dysfunctions because "treatment can be anchored to the solid foundation of an accurate diagnosis.

There is no evidence that the risk of cerebral angiography today is at all commensurate with the frequently grave risk to the patient of the condition for which the test is used," he concludes.

BAXTER INTRODUCES NEW DRUG

Urevert, a new drug, has produced dramatic results in treating head injuries and in brain surgery, Baxter Laboratories, Inc., Morton Grove, Ill., has announced.

The drug is a combination of sterile, lyophilized, synthetic urea and an invert sugar solution and is now available for use by neurosurgeons. Urevert can safely reduce increased intracranial pressure resulting from head injuries or brain tumors, thus facilitating treatment or surgery.

The new product, produced by Baxter's Travenol Laboratories division, is packaged as a unit of 2 containers—one holding sterile, lyophilized, synthetic urea under vacuum and the other containing the sterile invert sugar solution.

$100,000 WYETH GRANT

The Wyeth Fund for Postgraduate Medical Education has granted $100,000 to 20 medical schools and hospitals throughout the United States for the third straight year.

The grants are unrestricted, said Herbert W. Blades, president of Wyeth Laboratories, Philadelphia, and the recipients may use the funds to advance the cause of medical education in any way they see fit.

The grants, each for $5,000, went to the following institutions: Albany Medical College; Boston University; Bryn Mawr, Pa., Hospital; Creighton University; Albert Einstein College of Medicine; Emory University; Lenox Hill Hospital, New York City; University of Maryland; College of Medical Evangelists; University of Mississippi; University of Missouri; New York University; Seton Hall University; University of Texas; Southwestern Medical School; University of Utah; Vanderbilt University; University of Vermont; University of Washington; Wayne University; and Yale University.

DILATION OF MAJOR BLOOD VESSELS

Injection of isoxsuprine hydrochloride (Vasodilan), a vasodilator distributed by Mead Johnson & Co., Evansville, Ind., increases diameter in the major blood vessels supplying a monkey's brain within ten minutes. Vessels are made visible by infusing x-ray opaque dye into blood flowing into the brain.

withdrawn **apathetic** rejected **gloomy**
remorseful hopeless **listless** despairing
forlorn **somber** defeated
bitter crushed

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β-phenylisopropyl hydrazine supplied as the hydrochloride

Important new psychoactive agent—acts selectively on the brain to brighten outlook, raise spirits, rebuild self-esteem, revitalize depressed patients.

Lakeside Laboratories, Inc., Milwaukee 1, Wisconsin

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For detailed information, request Brochure No. 19, CATRON

Important New

Catron

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How to use this new drug:

CATRON Hydrochloride is a monoamine oxidase (MAO) inhibitor useful in the treatment of depression and of other disorders indicated below. It is recommended for use in carefully selected cases and in those patients who have not responded to the milder drugs.

ADMINISTRATION AND DOSAGE

Dosage of CATRON must be individualized according to each patient's response. The initial daily dose should not exceed 12 mg. and should be reduced as soon as the desired clinical effect is obtained. In severe depressions some clinicians desire rapid results and begin treatment with 24 mg. daily: this dosage should not be continued for more than a few days. A single daily dose in the morning is recommended. A continuous or interrupted schedule may be used, the latter during the maintenance period.

DEPRESSION (Endogenous, Reactive, Postpartum, Involutional and Depression Secondary to Schizophrenic or Neurotic Reaction): initially, 12 mg. once daily for approximately 2 weeks, or less if improvement appears. Dosage is then reduced to 6 mg. daily. As improvement continues, maintenance dosage of 6 mg. every other day or of 3 mg. daily often proves satisfactory. An interrupted dose schedule is recommended for long-term therapy.

ANGINA PECTORIS—3 to 6 mg. daily in most cases. Relief of pain and elevation of mood may be dramatic. Victims of angina pectoris who respond in this manner should be cautione against overexertion induced by their sense of well-bei

RHEUMATOID ARTHRITIS (Adjunctive Therapy—in severely d abling forms, particularly when accompanied by depre sion): 9 to 12 mg. daily for 3 days, then 6 mg. daily, reducin further to 3 mg. daily on signs of improvement. If a co ventional antiarthritic agent is used, lower doses of ea are indicated.

CAUTION

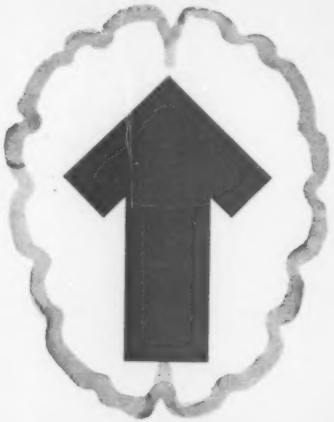
Certain circumstances should be watched carefully whe using CATRON.

DRUG POTENTIATION—The list of drugs which CATRON potent ates is not yet complete. CATRON should not be used co comitantly with any other drug unless, (a) it has be ascertained that the two drugs bear no qualitative relatio ship, or (b) potentiating action is being sought, as may b the case with tranquilizing drugs including reserpine a the phenothiazines, and with the amphetamines, barbitu rates and hypotensive agents.

HYPOTENSIVE EFFECT—All normotensive patients receivin CATRON, but especially elderly patients, should be warne about the possibility of orthostatic hypotension during th initial period of higher dosage. In the few instances whe this may occur, lowering of the dose will usually perm continuation of therapy.

COLOR VISION—A reversible red-green color defect has bee reported in a few patients, chiefly hypertensives, on

Psychoactive Agent



- Brightens mood, diminishes apathy and confusion, curbs symptoms of withdrawal, self-pity, inadequacy, despair.[1,2]
- Acts selectively on brain at doses having little or no effect on liver.[3-7]
- Valuable in depressions associated with chronic diseases such as angina pectoris,[8] severe rheumatoid arthritis.[9]

For detailed information, request Brochure No. 19, CATRON

tended therapy with CATRON. Discontinue the drug if such changes occur.

ANIMALS, NEUROLOGIC SIGNS—In toxicity studies with animals, a neurologic syndrome has been observed characterized by tremors, muscle rigidity and difficulty in locomotion. Although extensive clinical experience has not shown such reactions to be a problem in humans in recommended dosage, should a similar neurologic disturbance occur, the possibility of drug action should be considered.

SIDE EFFECTS—Major side effects requiring cessation of therapy are infrequent. Other side effects—constipation, delay in starting micturition, increased sweating, hyperreflexia, ankle edema, blurring of vision, dryness of the mouth—are usually readily controlled by lowering the dosage. Rash, observed in a few patients, cleared up rapidly upon discontinuing therapy.

WARNING: Pharmacologic studies show that with proper dosage CATRON will inhibit monoamine oxidase in the brain without influencing this enzyme in the liver. This is in contrast to previous inhibitors, which depress monoamine oxidase activity in the liver before affecting this enzyme in the brain.

Although the evidence suggests that serious life-threatening hepatitis seen with other MAO inhibitors should not occur with CATRON in the recommended dosage, it has been reported on rare occasion with dosages in excess of the recommended levels.

The Following Precautions are Recommended:

1. In all instances daily dose should not exceed 12 mg.
2. Reduce daily dose as soon as response is established, usually in a matter of 1 to 2 weeks.
3. Do not prescribe to a patient more than sixteen 6 mg. tablets or thirty-two 3 mg. tablets of CATRON at one time.
4. Patient should return for observation before additional CATRON is prescribed. For this reason, prescriptions for CATRON should be marked, "not refillable."
5. Perform regular liver function tests.
6. Do not use the drug in patients with a history of viral hepatitis or other liver abnormalities.

CATRON is the original brand of β-phenylisopropyl hydrazine. It is supplied as the hydrochloride in tablets of 3 mg. and 6 mg., bottles of 50.

(1) Agin, H. V.: The Use of JB-516 (CATRON) in Psychiatry, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958. (2) Bercel, N. A.: A Pharmacologic Approach to the Study of the Mind, Springfield, Ill., Charles C Thomas, 1959, in press. (3) Kinross-Wright, J.: Panel Discussion of Psychic Energizers, *ibid.* (4) Kinross-Wright, J.: Experience with JB-516 (CATRON) and Other Psychochemicals in Clinical Practice, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958. (5) Horita, A., and Parker, R. G.: Comparison of Monoamine Oxidase Inhibitory Effects of Iproniazid and Its Phenyl Congener, Proc. Soc. Exper. Biol. & Med. 99:617, 1958. (6) Horita, A.: Beta-Phenylisopropylhydrazine, A Monoamine Oxidase Inhibitor, Fed. Proc. 17:379, 1958. (7) Horita, A.: The Pharmacology of the Monoamine Oxidase Inhibitors, in A Pharmacologic Approach to the Study of the Mind, Springfield, Ill., Charles C Thomas, 1959, in press. (8) Kennamer, R., and Prinzmetal, M.: Treatment of Angina Pectoris with CATRON (JB-516), Am. J. Cardiol. 3:542, 1959. (9) Scherbel, A. L., and Harrison, J. W.: The Effects of Iproniazid and Some Other Amine Oxidase Inhibitors in Rheumatoid Arthritis, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958.

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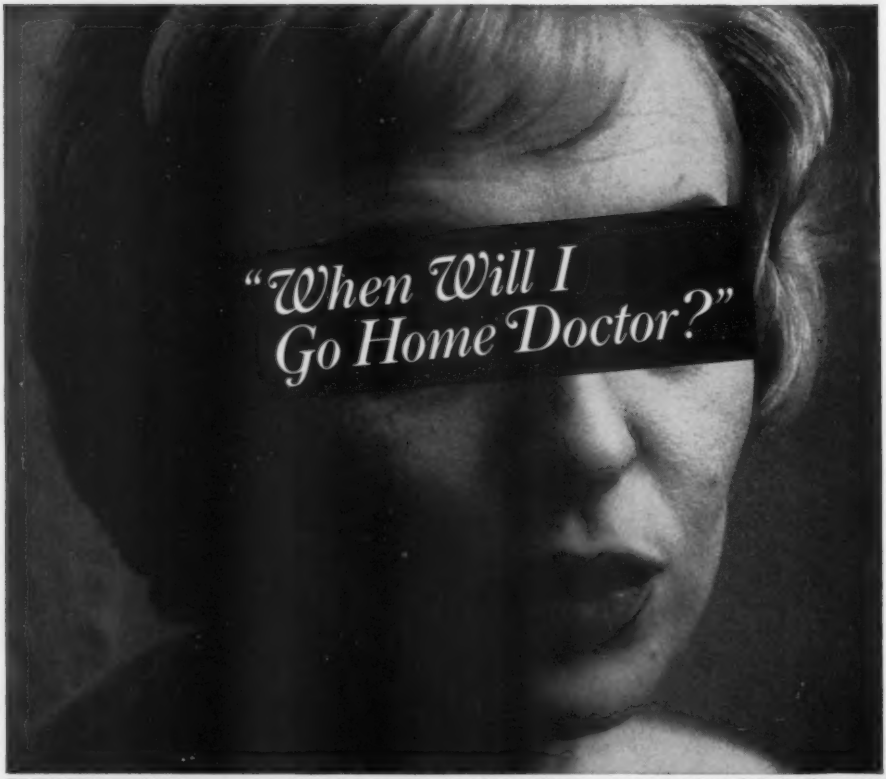

YOUR ANSWER MAY BE "I DON'T KNOW" OR "VERY SOON." VESPRIN MAY MAKE THE DIFFERENCE

Vesprin is an agent of established efficacy and demonstrated superiority for the management of psychotic patients. In schizophrenia, manic states, and psychoses associated with organic brain disease, Vesprin controls intractable behavior patterns making patients more accessible to psychotherapy. Excitement, panic, delusions, hostile behavior are moderated to permit early insight for rapid progress into resocialization and rehabilitation. Not only is Vesprin your drug of choice for initial therapy, but it has proved effective in patients who failed to respond to other phenothiazines.

Vesprin does not oversedate your patients into sleepiness, apathy or lethargy — and drug-induced agitation is minimal.[1] It is relatively free from side effects.[1,2] Skin eruptions, photosensitivity or hyperthermia have rarely been reported. Individual dosage levels are easily established. Intramuscular injection causes no pain or tissue irritation. Vesprin often brings improvement in chronically disturbed patients refractory to shock therapies and other drugs.[3,4]

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Dosage: Usual initial dose, 100 to 150 mg. daily, increased or decreased according to patient response. See literature. Supply: Tablets: 10, 25 and 50 mg., in bottles of 50 and 500. Capsules: 100 mg. in bottles of 50 and 500. Emulsion: 30 cc. dropper bottles and 120 cc. bottles (10 mg./cc.). Parenteral Solution: 1 cc. multiple dose vial (20 mg./cc.) and 10 cc. multiple dose vial (10 mg./cc.). Vesprin Injection Unimatic (15 mg. in 0.75 cc.).

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NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

Augustus S. Rose, M.D., President
A. L. Sahs, M.D., President-Elect
Joseph M. Foley, M.D., Vice-President
Robert Utterback, M.D., Secretary
Charles M. Poser, M.D., Treasurer

AUGUST 1959

Denny-Brown Becomes New ANA President

Derek E. Denny-Brown assumed the presidency at the close of the 84th annual meeting of the American Neurological Association at the Hotel Claridge, Atlantic City (June 15-17, 1959), succeeding Bernard J. Alpers. Other officers elected were: Harold G. Wolff, President-elect; Charles Rupp, First Vice-President; Samuel Brock, Second Vice-President; Melvin D. Yahr, Secretary-Treasurer and Editor of the Transactions; and Clark H. Millikan, Assistant Secretary. Elected to the ANA Council were Bernard J. Alpers, Alexander T. Ross (for two years), and Benjamin Boshes (for two years). A. L. Sahs was appointed as representative to the American Board of Psychiatry and Neurology. The program of the two-and-a-half day meetings brought forth 40 scientific papers, 7 scientific demonstrations, and 7 technical exhibits. The Monday afternoon session (June 15) was devoted to a joint session with the American Association of Neuropathologists, which comprised mostly considerations of the clinicopathologic aspects of vascular diseases of the nervous system. Among the distinguished foreign visitors at the meeting were: R. A. Henson (London); Shigeo Okinaka (Tokyo); and Antonio Subirana (Barcelona) ....At their executive sessions the Association voted to hold under their auspices in 1961 (independent of the annual meeting) a conference on cerebrovascular disease to be sponsored by the National Institute of Neurological Diseases and Blindness....The 85th annual ANA meeting will be held at the Statler Hotel, Boston, June 13-15, 1960.

Foley To Take Post At Seton Hall

Joseph M. Foley, Assistant Professor of Neurology at Harvard University and Vice-President of the American Academy of Neurology, will take over his new duties as Professor of Neurology at the Seton Hall College of Medicine and Dentistry, Jersey City, sometime during the first week of September 1959. When queried about his plans, in true laconic fashion, Foley replied, "My hope is that we will have a neurological staff going 'full tilt' by July 1960. This may be optimistic, and I will not be disappointed if I cannot realize this objective until 1961."

Mental Retardation To Be the Subject at Next ARNMD Meeting

The problems of mental retardation will provide the principal topic under discussion at the 1959 meeting of the Association for Research in Nervous and Mental Disease,

Inc., to be held at the Hotel Roosevelt, New York City (December 11-12, 1959). The present officers of the Association are Lawrence C. Kolb, President; Richard L. Masland, Vice-President; Robert E. Cooke, Vice-President; and Rollo J. Masselink, Secretary-Treasurer, 700 West 168th Street, New York 32....The present membership of the ARNMD lists 783 active, 6 sustaining, 28 senior, and 88 associate members.

Neuropathologists Meet in Frankfurt Official delegates to the planning reunion of the Fourth International Congress of Neuropathology met in Frankfurt-am-Main (June 4, 1959) to structure their program of their 1961 Congress in Munich. The 1961 Congress will continue for four and one-half days (September 4-8), terminating shortly before the Seventh International Neurological Congress (Rome, September 10-16, 1961). The Congress of Neuropathology will open Sunday, September 3, for registration and an official welcome. Monday, Tuesday, and Wednesday mornings (September 4-6) will be devoted to a consideration of three major topics: histochemistry and the related biochemistry of diseases of the central and peripheral nervous systems; electronmicroscopy of the central and peripheral nervous systems and of the myoneural junction; and cell biology and cell culture of nervous tissue. The directors of these topics will be announced later. Discussions and formal reports related to the three major topics will be presented at parallel sessions during the afternoons of the first three days. A program of free communications will be conducted during the afternoons of all four days. These presentations also are to be grouped according to subject matter under various topics, directed by a chairman. The morning of the fourth day (September 7) will be devoted to a discussion of perinatal neuropathology, and the morning of the fifth day (September 8) will be held in conjunction with an International Association of Neuroanatomists, with emphasis on comparative neuroanatomy (Spatz and Verhaart).... Elected as Honorary Presidents to the Congress were Ludo van Bogaert (Belgium) and Ivan Bertrand (France). The Secretary-General is Professor Dr. Hans Jacob, Direktor der Nervenklinik der Universität Marburg, Ortenbergstrasse, Marburg/L., Germany. Chairman of the United States National Committee is Orville T. Bailey, Professor of Neurology, University of Illinois School of Medicine, Chicago.

WFN Executive Committee Deliberates in Rome On Sunday afternoon, June 7, 1959, at the Istituto Superiore di Sanità in Rome, the Executive Committee of the World Federation of Neurology convened for their first annual meeting under the presidency of Ludo van Bogaert. Also present as observers were Henri Gastaut (Marseille) and J. Radermecker (Belgium), both representing the International Federation of Electroencephalography and Clinical Neurophysiology; and Mario Gozzano, Chairman of the Italian national organizing committee of the Seventh International Neurological Congress....President van Bogaert opened

the meeting with a report of progress made by the Federation since its original organizational meeting held in Brussels, July 1957. He described the Federation's achievements to date in sponsoring international symposia and in formulating projects for international collaborative research. He spoke of the progress made in the organization of problem commissions in specialized fields, that is, neuropathology, neurochemistry, comparative anatomy and pathology, geographic neurology, and electroencephalography, where problems existed which are vulnerable to a programmed attack. He also spoke of the advances made in the organization of the WFN Secretariat as a repository and exchange center of scientific information and laboratory specimens. He predicted the important future role of the WFN in organizing international symposia and congresses and in helping younger neurologists to participate in future congresses. He thanked H. Houston Merritt, Pearce Bailey, and the National Institute of Neurological Diseases and Blindness for their assistance in making the WFN a reality. Finally, President van Bogaert presented the first Newsletter of the WFN and proposed WFN support of a monthly journal, WORLD NEUROLOGY. He also proposed the organization of a permanent secretariat in Antwerp with a full-time staff and requested that he be empowered to designate a local or national secretary of each constituent country to serve as the direct liaison with the permanent secretariat....The Executive Committee unanimously approved all the proposals and recommendations of President van Bogaert including an official WFN journal, WORLD NEUROLOGY, with a monthly Newsletter and the revised Constitution....Charles M. Poser, WFN Executive Medical Officer, was elected Editor-in-Chief of WORLD NEUROLOGY.

Preliminary Plans Made for 7th International Neurological Congress

On June 8, 1959, official delegates of the national neurologic societies composing the Seventh International Neurological Congress convened in Rome to draw up a preliminary scientific program for this congress to be held in the same city (September 10-16, 1961*). These planning sessions took place in the Aula Magna of the Istituto Superiore di Sanità in Rome. According to present plans, the inauguration ceremonies will take place Sunday afternoon, September 10, and on the same afternoon joint sessions will be held with the Ninth Congress of the International League Against Epilepsy. The activities of the Congress will continue until Saturday, September 16, one free day (Wednesday, September 13) having been set aside for excursions and sight-seeing. Tuesday evening, September 12, has been reserved for the delegates to choose the site of the Eighth International Neurological Congress. The General Assembly will be convocated either Friday afternoon, September 15, or Saturday afternoon, September 16....The scientific program will highlight three principal topics: cerebrovascular disorders associated with cardiopulmonary disease (Monday, September 11),

*Erroneously reported as 1960 in the July issue of this Newsletter.

endogenous metabolic and toxic disorders of the nervous system (Tuesday, September 12), and language disorders (Thursday, September 14). The respective topic directors elected to organize these symposia are G. Bodechtel (Germany); H. Houston Merritt (U.S.A.), and Macdonald Critchley (United Kingdom). The Monday and Tuesday sessions (September 11 and 12) will be held jointly with the Fifth International Congress of Electroencephalography and Clinical Neurophysiology. Friday, September 15, was selected as the day for the presentation of free communications in which the digest system (grouping of presentations according to subject matter) of reporting will be used. The official languages of the Congress will be English, French, German, and Italian....Professor Paul Van Gehuchten of Louvain was elected Honorary President of the Congress, and Professor Mario Gozzano, Acting President. Professor Gozzano was empowered to appoint the other officers (their names to be announced later) of the Italian organizing committee. The offices of the secretariat of the Congress are in the Clinica Neurologica, Viale Dell'Universita, 30, Rome....The following registration fees were fixed: active members, $15; associate members, $10; and guests, $5....The Congress will be held under the auspices of the World Federation of Neurology and the National Institute of Neurological Diseases and Blindness.

Briefs Webb Haymaker is the newly elected President of the Association of American Neuropathologists....Dr. A. Minkowski, Director and Head of Research at the National Institute of Hygiene of the University of Paris, was a guest of the National Institute of Neurological Diseases and Blindness and gave a lecture (July 17) on "Neurophysiology and EEG during Fetal Life."....The Fifth International Medical Conference, to be sponsored by the National Foundation, will be held in London, July 18-22, 1960, on the subject of congenital malformations, with some 50 nations expected to participate....The United Epilepsy Association has announced the award of an initial grant for an extensive research project in epilepsy at the Neurological Institute of New York. The project will be under the direction of H. Houston Merritt and Melvin D. Yahr....The dates for the 1960 annual meeting of the AAN are April 25-30 and not April 21-26 as reported in the May issue of the Newsletter.

Percy Bailey

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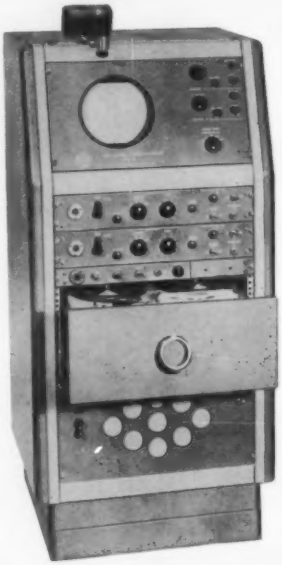

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NOW...
TINY TABLET UNDER TONGUE
STOPS MIGRAINE
'SICK' RECURRENT HEADACHE
FAST
SHUTS OFF PAIN
BLOCKS OUT FEAR
ANYTIME, ANYWHERE, WITHOUT NEED EVEN FOR A GLASS OF WATER

because prodromal warning usually tells patients that the time to arrest imminent migraine attack is right now, and the place to do it is right here.

NEW **ergomar**™

SUBLINGUAL ERGOTAMINE TARTRATE TABLETS

MORE CONVENIENT... NO WATER, INJECTIONS OR PRIVACY NEEDED

All the patient has to do is to place a tiny ERGOMAR tablet under tongue. It enters blood stream directly through buccal lining, bypasses stomach and hepatic system and aborts vascular headache and migraine in approximately one half the usual time of ingested tablets.[1-5]

Dosage: Sublingually, 1 tablet at onset of attack. Additional doses may be taken, if necessary, as follows: 1 tablet every half-hour until relief is obtained. Total dosage must not exceed 3 tablets within 24 hours.

Contraindications: Peripheral vascular and coronary heart disease, hypertension, renal or hepatic dysfunction and pregnancy.

Supplied: ERGOMAR Tablets, 2 mg. ergotamine tartrate per tablet, in specially developed dispenser packages of 12 tablets. *May we suggest for patient convenience and economy, writing for not less than 12 tablets in a prescription.*

References: 1. DeJong, R. N.: GP *19*:147, 1959. 2. Scientific Exhibit, 9th Annual Meeting, Am. Acad. Neurology, Boston, Mass., April 22-27, 1957. 3. Berman, B. A.: Current personal communication in the files of Nordson Laboratories. 4. Saunders, S. H.: Current personal communication in the files of Nordson Laboratories. 5. Blumenthal, L. S., and Fuchs, M.: Am. Acad. Neurology, Los Angeles, Calif., April 15-18, 1959. *Sublingual Administration of Ergotamine in Relief of Migraine and Vascular Headache.*

ERGOMAR™ brand of specially processed ergotamine tartrate*

NORDSON PHARMACEUTICAL LABORATORIES, INC. / 35A ELLIS AVENUE, IRVINGTON, N. J.
(formerly Nordmark)

*PAT. PENDING